Generation and Trapping of Pyridine *o*-Quinodimethanes and Their Functional Analogues: Synthesis of Heterolignans and Conformationally Restricted Analogues of Nicotine

Thesis submitted to the
Indian Institute of Technology, Kharagpur
For the Degree of
Doctor of Philosophy

By

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INDIA

Dedicated to

My Parents and my Brother

Continuous effort, not strength or intelligence

is the key to unlocking our potential

Liane Cardes

Tarun K. Sarkar

Professor of Chemistry

Certificate

*This is to certify that the thesis entitled "**Generation and Trapping of Pyridine o-Quinodimethanes and Their Functional Analogues: Synthesis of Heterolignans and Conformationally Restricted Analogues of Nicotine**" being submitted by Niranjan Panda to the Indian Institute of Technology, Kharagpur, India, for the award of the degree of Doctor of Philosophy is a record of bonafide research carried out by him under my supervision and guidance. I am satisfied that the thesis has reached the standard fulfilling the requirements of the regulations relating to the nature of the degree. The contents of the thesis have not been submitted for the award of any other degree or diploma.*

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Finally, I wish to thank all of my friends for making my stay in this institute a memorable experience. Without their inspiration, help and encouragement this work would not have been possible.

Date: *Niranjan Panda*

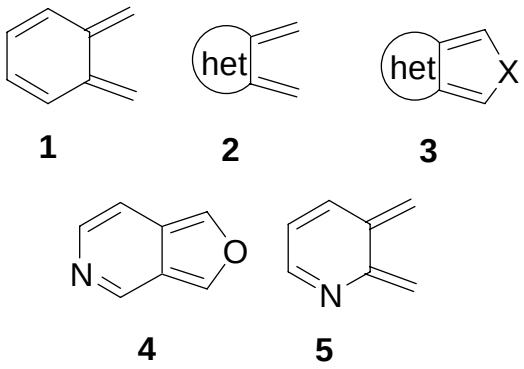
Biography

Mr. Niranjan Panda was born at Olang (Bhadrak), Orissa, India on June 21, 1976. He received his B. Sc. Degree with Honours in Chemistry in 1996 from Bhadrak College, Utkal University, Orissa. In 1998, he received his M. Sc. Degree from Ravenshaw College (Autonomous), Cuttack, Orissa. In M. Sc. Program he was awarded "Narayanee Mohanty Prize" for scoring highest percentage of marks for the year 1998. He joined in the Department of Chemistry, Indian Institute of Technology, Kharagpur in the year 2000 as a Junior Research Fellow. After completion of about three years he was awarded a "Senior Research Fellowship" from CSIR, Government of India, New Delhi. During his doctoral program at Indian Institute Technology, Kharagpur, he has published papers in internationally reputed journals.

His area of research interests includes Synthetic Organic and Organometallic Chemistry, Heterocyclic Chemistry and Bioorganic Chemistry.

Abstract

Since Cava's pioneering work on the generation of the very reactive species *o*-quinodimethane **1**, studies have continued unabated on the modes of preparation, physical properties, and synthetic applications of **1** and its derivatives. Several review articles published during the past few decades amply bear this out. On the other hand, the heteroaromatic analogues **2** have received much less attention, although this situation is rapidly changing in recent years. In the background of this development, it is surprising that not much systematic work has been done on functional analogues of **2**, e.g. **3** (X = O), which are good candidates for both inter- and intramolecular Diels-Alder reactions leading to an array of heterocyclic ring systems related to natural and non-natural products of biological significance.



The present research has essentially addressed this issue involving both **4** and **5**, details of which are described in this thesis entitled "**Generation and Trapping of Pyridine *o*-Quinodimethanes and Their Functional Analogues: Synthesis of Heterolignans and Conformationally Restricted Analogues of Nicotine**."

The thesis is divided into two chapters, Chapter 1 and Chapter 2.

Chapter 1

This chapter demonstrates that sequential Pummerer-Diels-Alder reaction is suited to efficient synthesis of a variety of heterocyclic ring systems including the potentially bioactive heterolignans. Thus, the Pummerer reaction of an *o*-benzoyl-substituted pyridylmethyl sulfoxide generates an α-thiocarbocation the interception of which by a neighboring keto functionality produces an α-thiosubstituted furo[3,4-*c*]pyridine as transient intermediate; the latter undergoes a Diels-Alder cycloaddition with an added dienophile. Base-induced ring opening of the cycloadduct followed by aromatization gives an isoquinoline derivative that may be looked upon as a heterocyclic analogue of 1-arylnaphthalene lignans. The facility of the sequential Pummerer-Diels-Alder reaction hinges on the experimental conditions, the best results being obtained with heptafluorobutyric anhydride as the triggering agent in toluene containing a catalytic amount of *p*-toluenesulfonic acid. In the absence of a dienophile it is possible to isolate and characterize a rather unstable furo[3,4-*c*]pyridine derivative. An intramolecular variant of this protocol is also feasible with use of unactivated alkenyl tethers of variable length. The usefulness of the sequential Pummerer-Diels-Alder reaction is further demonstrated through the synthesis of a heterolignan with a built-in lactone ring via oxidation of the initial [4+2]-cycloadduct followed by extrusion of phenyl sulfinate and elaboration of the resulting hydoxylated isoquinoline derivative.

Chapter 2

This chapter deals with the trapping of pyridine *o*-quinodimethanes generated by a formal imine-tautomerisation route. Thus, reactions of appropriately substituted

pyridine-derived imines having an *ortho* methyl/phenylsulfanylmethyl group with methyl chloroformate in the presence of Hünig's base generates transient pyridine *o*-quinodimethane intermediates which undergo intramolecular Diels-Alder reaction leading to conformationally restricted analogues of nicotine. That the success of this reaction hinges on the presence of a phenylsulfanyl group in the pyridine sidearm has been demonstrated as in the earlier investigation reported from this laboratory. Recently, conformationally constrained nicotines of the type described in this chapter have become targets of intensive investigation in view of their potential use for the treatment of various central nervous system (CNS) disorders including Alzheimer's disease, Parkinson's disease and depression.

Contents

General Details

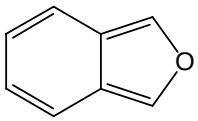
All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: Tetrahydrofuran (THF), benzene, toluene, xylene and diethyl ether (Et_2O) from sodium benzophenone ketyl; dichloromethane (CH_2Cl_2), carbon tetrachloride (CCl_4) and acetonitrile (CH_3CN) from P_2O_5; DMSO and DMF from CaH_2; Et_3N, pyridine, and diisopropylamine from solid KOH; and methanol from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (Acme's, particle size 100-200 mesh, SRL 60-120 mesh) using ethyl acetate petroleum ether (60-80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plate (silica gel GF_{254} and silica gel G, Merck). ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker AC 200 spectrometers using $CDCl_3$ and mixture of $CDCl_3$ and CCl_4 as solvent and in some cases DMSO-d_6. Tetramethylsilane (TMS) was used as internal standard (0.0 ppm) in some cases, otherwise $CHCl_3$ (in $CDCl_3$) was used as an internal standard (7.25). Chemical shifts are reported in ppm downfield (δ) from Me_4Si. Coupling constant (J_{value}) were given in Hz. The abbreviation used for ^{1}H- and ^{13}C-NMR multiplicities follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) doublet of doublet and (bs) broad singlet.

Chapter 1

A Sequential Pummerer-Diels-Alder Route for the Generation and Trapping of Furo[3,4-*c*]pyridines: Synthesis of Heterocyclic Analogues of 1-Arylnaphthalene Lignans

1. Introduction

Isobenzofurans represented by benzo[*c*]furan (**1**) have for a long time served as an interesting class of reactive intermediates in organic synthesis. As functional analogues of *o*-xylylenes, they take part in both inter- and intramolecular Diels-Alder reactions leading to a variety of polycyclic ring systems including natural products of biological significance.[1] In contrast, heteroanalogues of isobenzofurans have received much less attention, although this situation is changing in recent years.[2,3]



1

The heteroaromatic isobenzofurans reported to date include furo[3,4-*b*]furans (**2**),

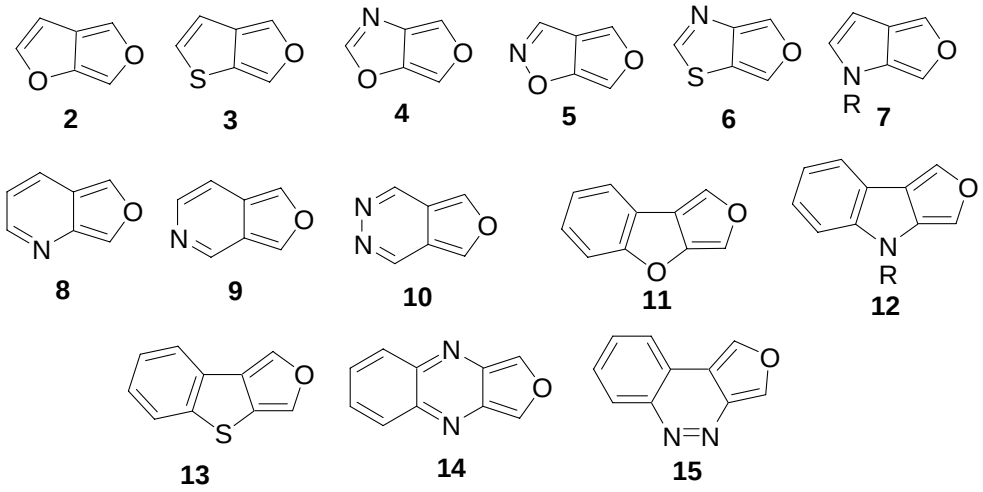


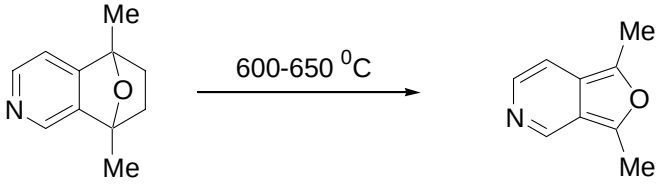
Figure 1

thieno[2,3-*c*]furans (**3**), furo[3,4-*d*]oxazoles (**4**), furo[3,4-*d*]isooxazoles (**5**), furo[3,4-*d*]thiazoles (**6**), furo[3,4-*b*]pyrroles (**7**), furo[3,4-*b*]pyridines (**8**), furo[3,4-*c*]pyridines (**9**), furo[3,4-*d*]pyridazines (**10**), furo[3,4-*b*]benzofurans (**11**), furo[3,4-*b*]indoles (**12**), benzo[4,5]thieno[2,3-*c*]furans (**13**), furo[3,4-*d*]quinoxalines (**14**) and furo[3,4-

c]cinnolines (**15**) (Figure 1).[3, 4] The parent members of most of the heteroaromatic isobenzofurans as shown in Figure 1 are as yet unknown except **9** and **10**. *However, stable derivatives of a number of heteroaromatic isobenzofurans have been made*. In this chapter a brief overview on the methods of generation of heteroisobenzofurans and their applications to the synthesis of natural products and non-natural products, especially heterolignans is presented.

1.1. Generation of heteroisobenzofurans

Over the years various methods[3] have been developed for the generation of heteroaromatic isobenzofurans which include flash vacuum pyrolysis[5, 6] (eq. 1 & 2), acid catalyzed cyclization[7] (eq. 3); Grignard reagent promoted cyclization[8] (eq. 4); Hamaguchi-Ibata reaction[9] (eq. 5) and Pummerer reaction[10] (eq. 6; see also section 2). A recent addition to this group includes the synthesis of some furo- and thieno[2,3-*c*]-fused heterocycles by reacting non-stabilized and stabilized phosphorous ylides with 2-acetyl-5-bromothiophene and 2-acetyl-5-methylfuran.[11]



eq. 1

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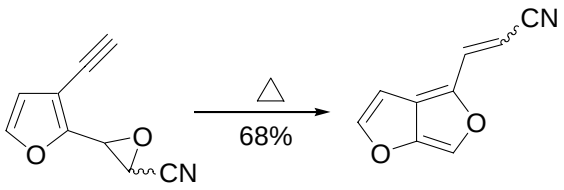

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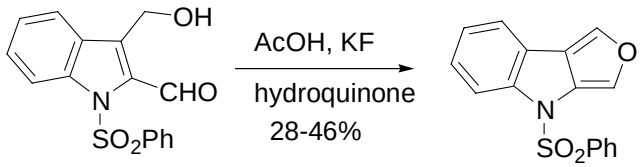

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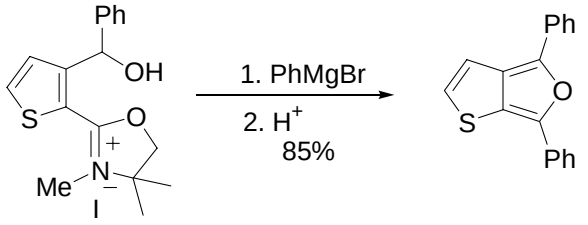
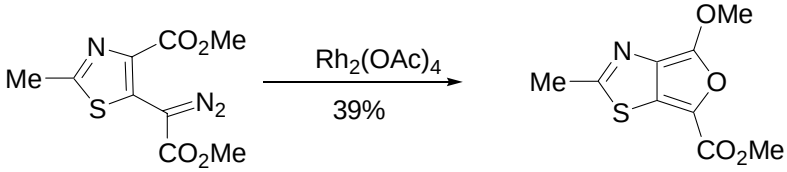
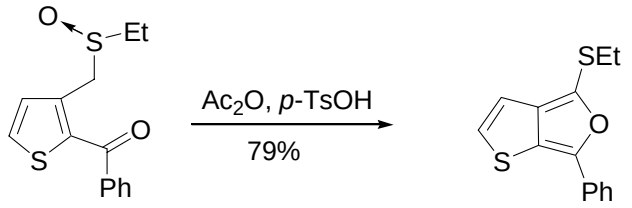


eq. 4



eq. 5



eq. 6

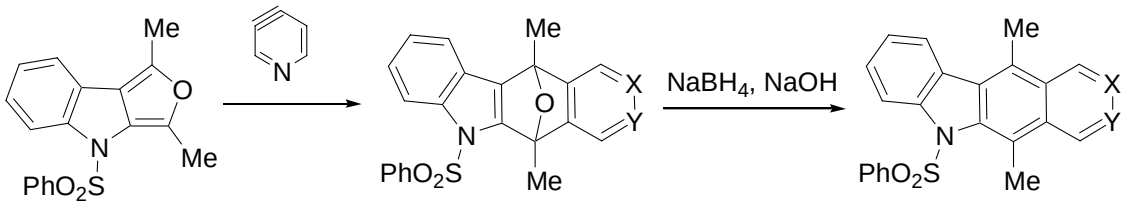
1.2. Application of heteroisobenzofurans

Unlike isobenzofurans, heteroisobenzofurans have not found as much use in the synthesis of natural and non-natural products. However, the limited work published in the literature is summarized here.

Ellipticine

One of the most interesting applications of heteroisobenzofurans is found in a synthesis of the potent anticancer pyridocarbazole alkaloid ellipticine (**19**). Thus, Gribble *et al*.[7] utilized the cycloaddition of **16** with 3,4-pyridynes which gave a 1:1 mixture of two regioisomeric products. Treatment of the mixture with $NaBH_4$ gave ellipticine **19** and isoellipticine **20** (Scheme 1).

Scheme 1



16

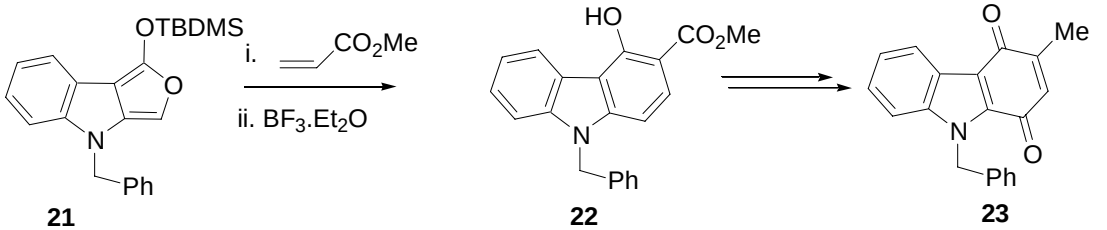
17; X = N, Y = CH
18; X= CH, Y = N

19; X = N, Y = CH
20; X= CH, Y = N

Murrayaquinone A

In 1993, Miki and Hachiken[12] synthesized Murrayaquinone A (**23**) via the regioselective cycloaddition reaction of furo[3,4-*b*]indole **21** with methyl acrylate (Scheme 2).

Scheme 2



21

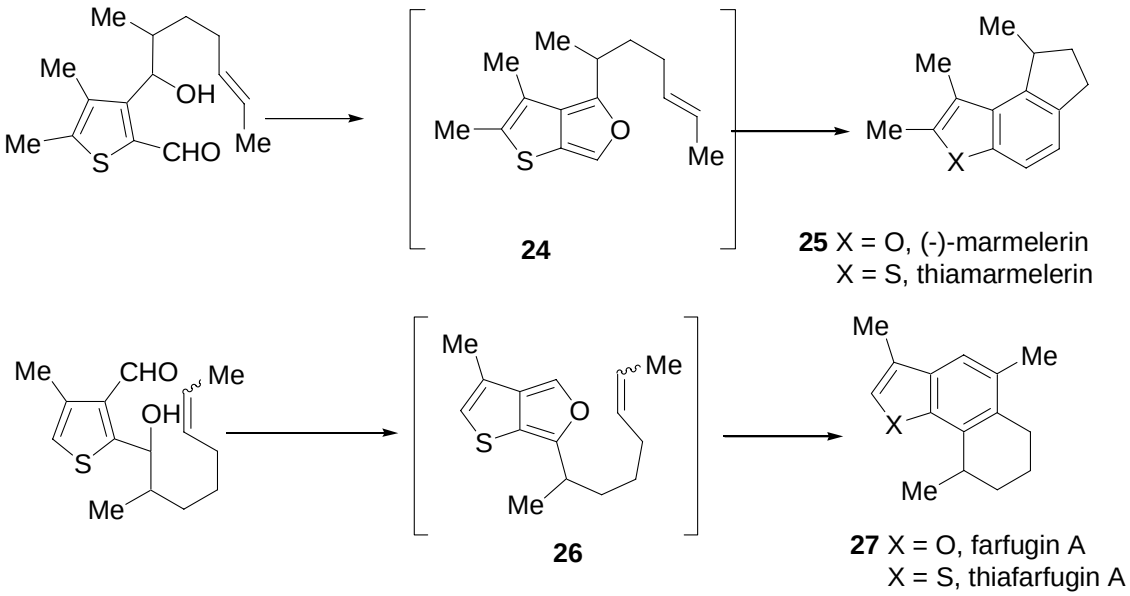
22

23
Murrayaquinone A

Thiamarmelerin and thiafugin A

Sulfur analogues of the furanosesquiterpenes (-)-marmelerin (**25**) and farfugin A (**27**) have been prepared using intramolecular Diels-Alder reactions of thieno[2,3-*b*]furans **24** and **26**, respectively (Scheme 3).[13]

Scheme 3



Heterolignans

Heteroaromatic isobenzofurans have also been used as potential building blocks for the synthesis of heterolignans. In this subsection it is deemed important to discuss the chemistry of heterolignans, and not just their synthesis as this is relevant to the work presented in this chapter.

The term heterolignan was first introduced by Ramos et al.[14] to define a class of compounds developed in a research line directed at the synthesis of new analogues of the

naturally occurring and biologically significant lignans, the main structural types of which is shown in Figure 2. Heterolignans are those synthetic analogues of lignans

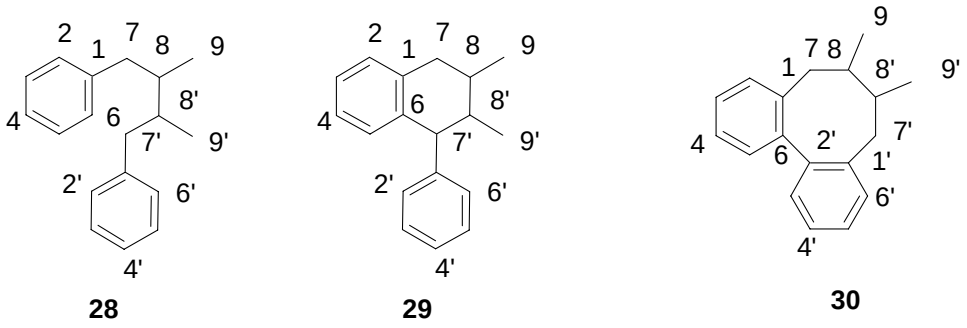


Figure 2

designed as a result of replacing of one or more carbon atoms of the propane moieties (C7-C9 and/or C7′-C9′) by heteroatoms and/or replacing one or both benzenic rings (C1-C6 and/or C1′-C6′) by heteroaromatic systems. The antitumor agent podophyllotoxin (**31**) and two of its semisynthetic derivatives etoposide (**32)** and teniposide (**33**), belong to the class of 1-arylnaphthalene lignans [15] (cf. **29** in Figure 2) (Figure 3). Although these

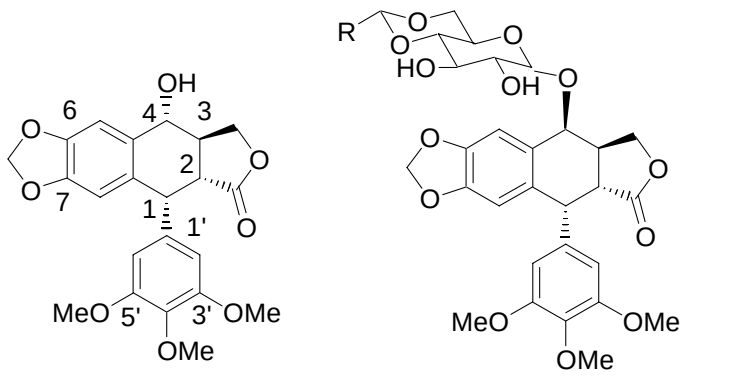


Figure 3

compounds have been used in front-line cancer therapy,[16] their therapeutic uses are often hindered by problems such as poor bioavailability, myelosuppression, and acquired drug resistance.[17] With a view to improving clinical efficacy and to overcoming the aforementioned problems a vast number of heteroanalogues of podophyllotoxin have been made and biological studies carried out.[18] Although not comprehensive a list of such analogues is given in Figure 4.[19] Of these compounds azatoxin **47**, a hybrid molecule of

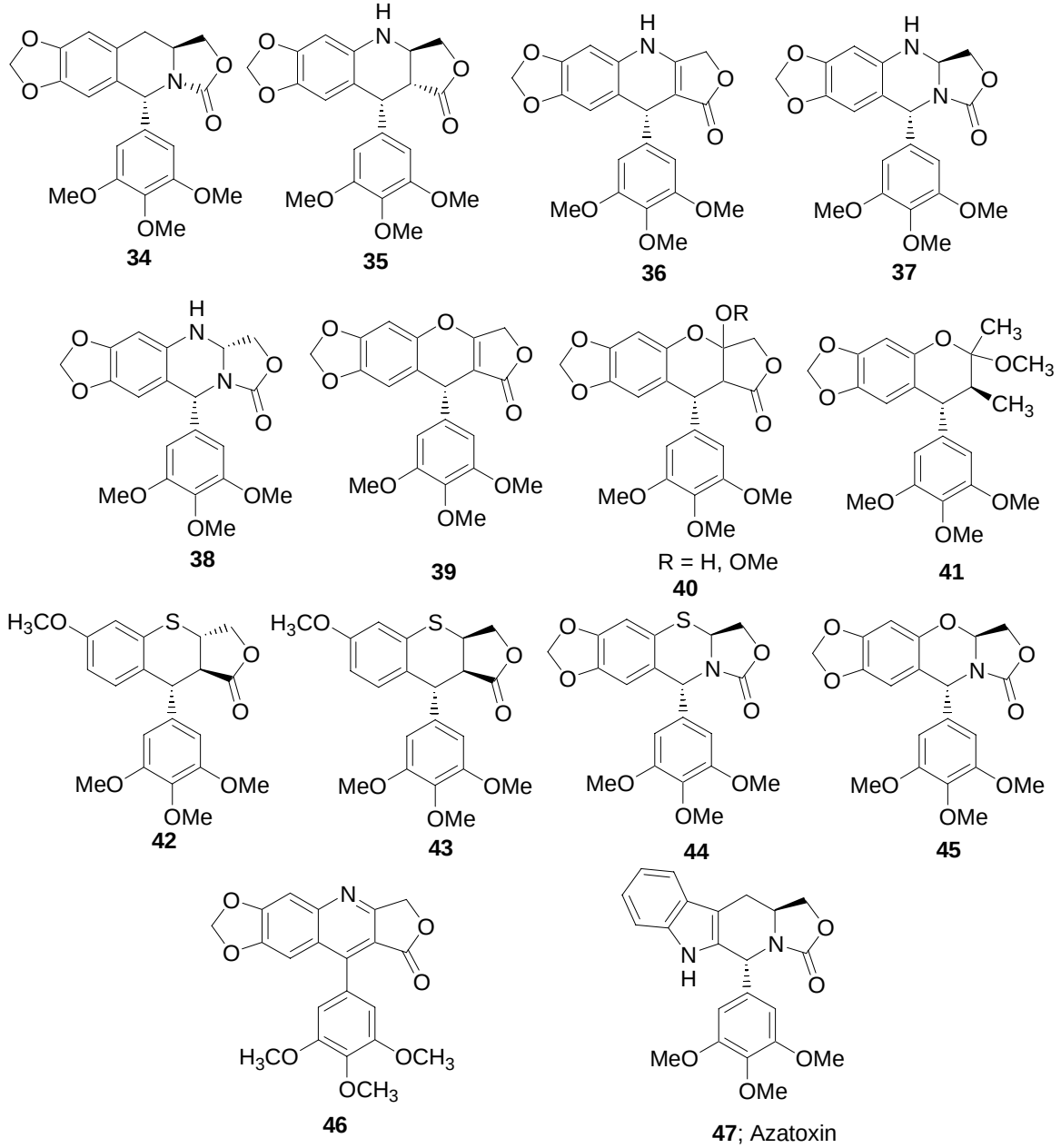
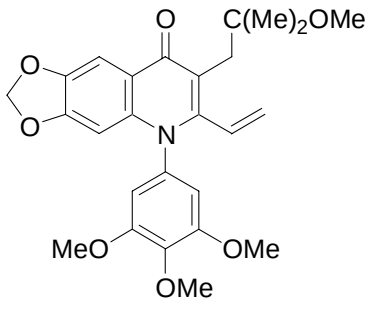


Figure 4

ellipticine and etoposide[20] has generated a lot of interest in view of its biological activity.[21] In fact it not only halts tubulin polymerization at variable concentrations but also acts as a potent inhibitor of DNA topoisomerase II, another target for anticancer agents. *It seems that current challenges in heterolignan research centers around synthesizing more such hybrid molecules and investigating their biological activities*. Thus, a synthesis of **48**, (Figure 5), a hybrid of antibacterial 4-quinolone and antitumor epipodophyllotoxin was developed.[22] Indeed it presents significant antiproliferative activity to human cancer cell lines (Hela cells and HL 60 leukemia cells) *in vitro* at 10^{-5} M. More recently, Zhao et al.[23] synthesized **49**, a hybrid of 1-arylnaphthalene lignan with isoquinoline alkaloid and its biological evaluation displayed apparent cytotoxicity against the A549 cell line with an IC_{50} value of 5.93 μM. Similarly, bio-assay of **50** shows anti-inflammatory potency in an adjuvant arthritis (AA) rat model.[24]



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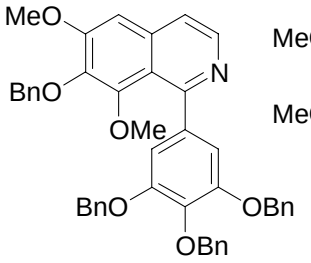

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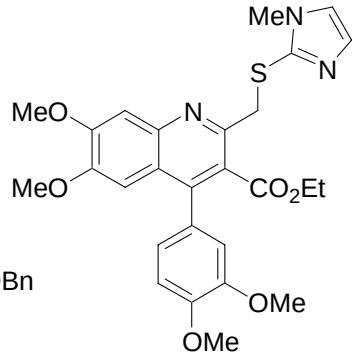


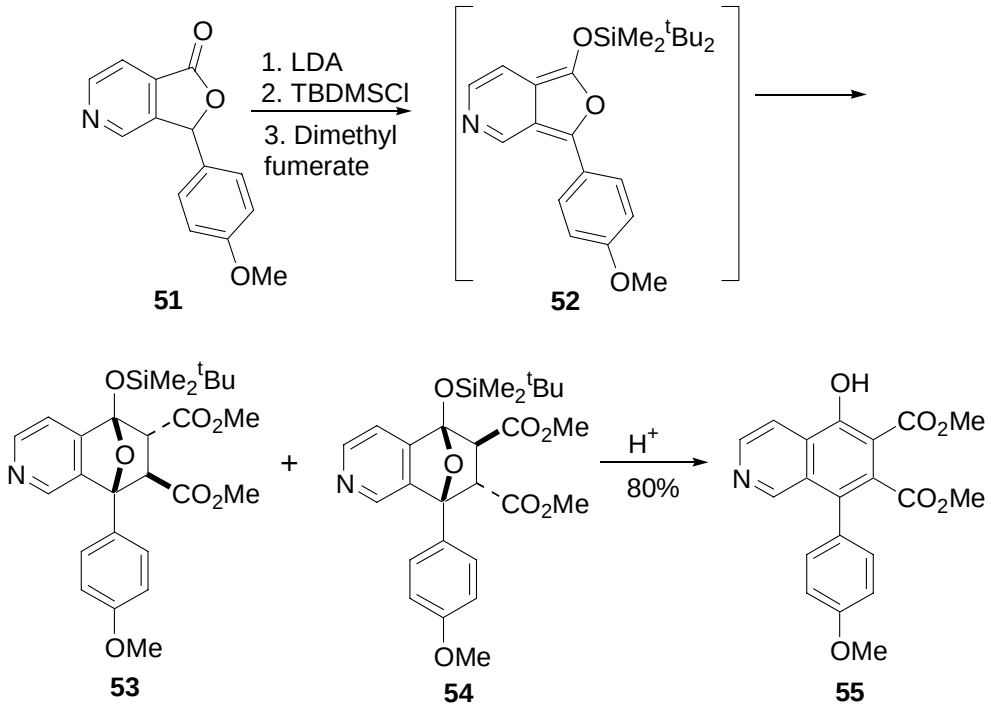
50

Figure 5

For synthesis of hetero analogues of 1-arylnaphthalene lignans azaisobenzofurans have found use as potential building blocks. The first synthesis of heterolignan **55**

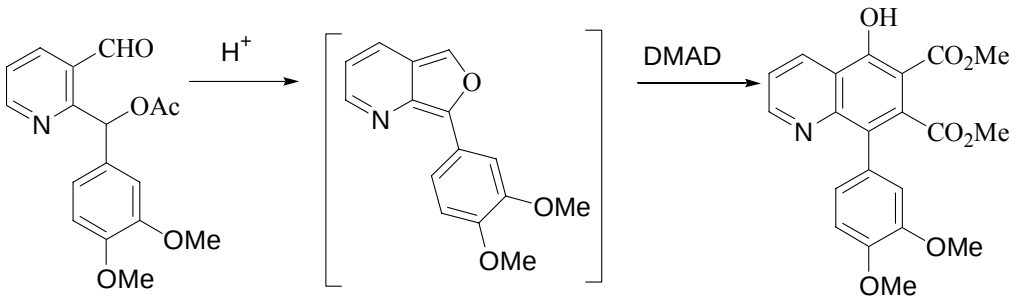
reported by Iwoa et al.[25] in 1984, involves the generation of furopyridine **52** as shown in Scheme 4. Interception of **52** with dimethyl fumerate led to **53** and **54** which were elaborated to heterolignan **55**.

Scheme 4



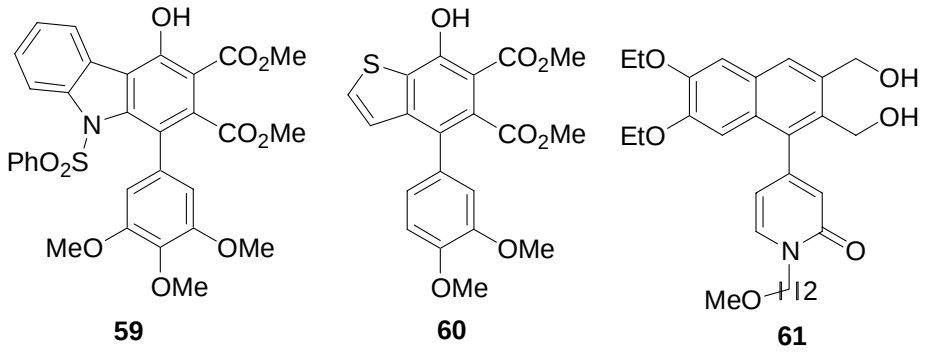
Iwasaki and co-workers[26] have reported another route for the synthesis of 1-arylquinoline lignans. Thus **56**, on treatment with a catalytic amount of trifluroacetic acid produced a carbocation which upon intramolecular cyclization and subsequent deprotonation generated the furo[3,4-*b*]pyridine **57**. Interception of **57** with dimethylacetylenedicarboxylate (DMAD) led to the formation of the desired lignan derivative **58** (Scheme 5). This methodology is also suitable for generation of thieno- as well as indole- derived 1-arylnaphthalene lignans (**59** and **60**) via the intermolecular Diels-Alder reaction of the *in situ* generated thieno[3,4-*b*]furan and furo[3,4-*b*]indole, respectively (Figure 6).[26]

Scheme 5



56 **57** **58** (66%)

Furthermore, via this protocol a series of 1-pyridylnaphthalene lignans was also made and evaluated for their ability to selectively inhibit PDE IV isolated from guinea pig. Thus, Iwasaki et al. found that the compound **61** shows potent antispasmogenic activity (ED_{50} = 0.08 mg/kg iv) without producing significant changes in heart rate with the use of histamine-induced bronchospasm assay.[27]



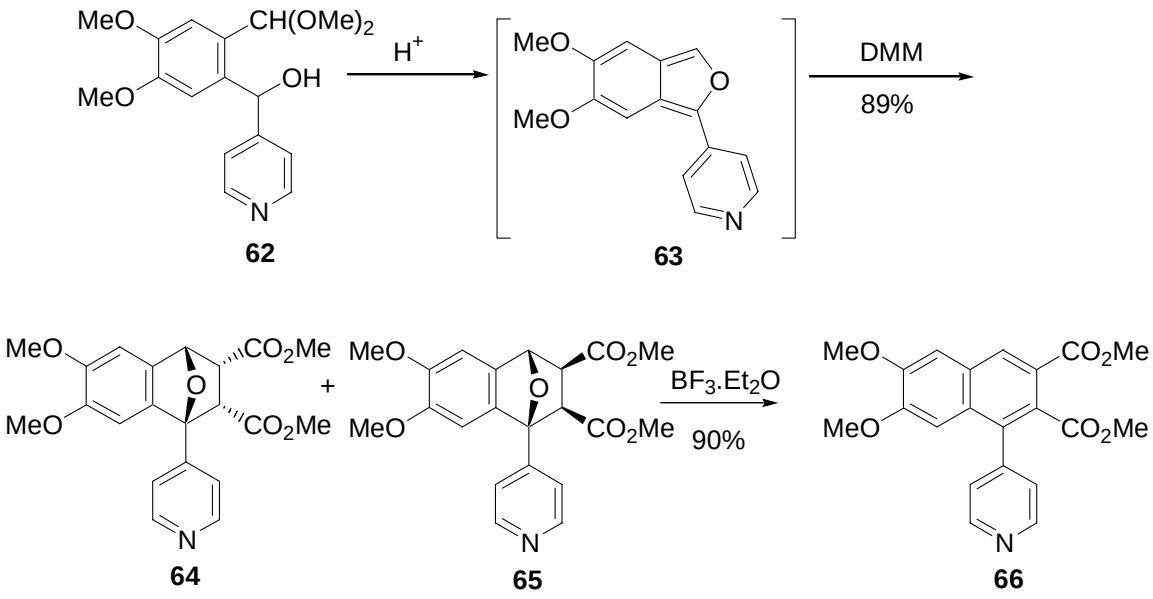
59 **60** **61**

Figure 6

Kappe and Padwa have made very elegant use of a tandem Pummerer-Diels-Alder reaction to access heteroanalogues of 1-arylnaphthalene lignans; however, *this work is presented in details in Section 2.*

More recently, Sugahara *et al*.[28] also reported the acid catalyzed transformation of pyridine substituted hydroxy acetal **62** to 1-pyridylisobenzofuran intermediate **63**; the latter undergoes rapid Diels–Alder reaction with dimethyl maleate to give **64** and **65** as a mixtures (1:1.3) of *exo* and *endo* diastereoisomers (Scheme 6). Treatment of **64** and **65** with $BF_3.Et_2O$ gave 1-pyridylnaphthalene lignan **66**.

Scheme 6



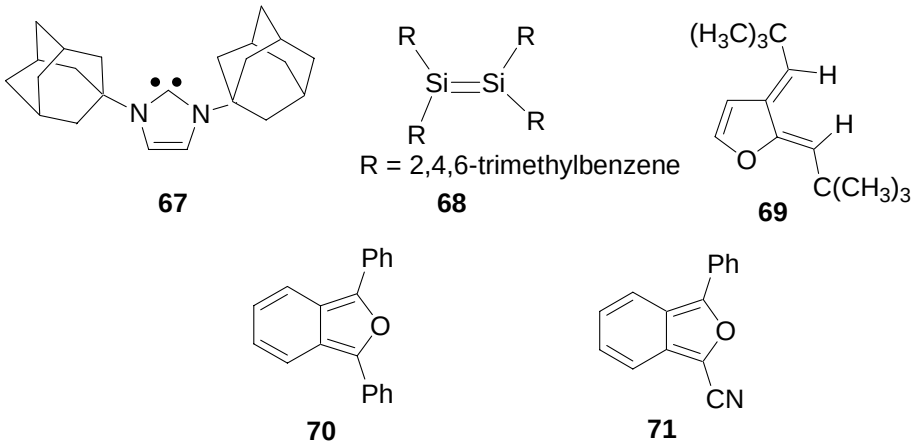
Besides the above mentioned routes, several other approaches have been made towards the synthesis of heterolignans.[14] However, this is outside the scope of this overview and hence no discussion in this regard is warranted.

2. Previous work from this laboratory

In our laboratory a comprehensive programme was initiated a few years ago to develop new and efficient methods for the generation of heterocyclic analogues of

isobenzofuran, e.g. furo[3,4-*c*]pyridine and demonstrate their use in the synthesis of various heterocyclic ring systems of biological importance.

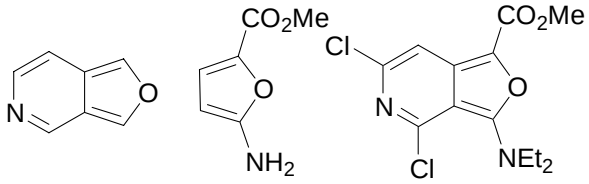
One of the major goals in organic synthesis is to make stable derivatives of the so-called "reactive intermediates." For example, the first stable or should we say a 'bottlable carbene' **67** was reported by Arduengo[29] in 1991 (Figure 7). Other examples include the crystalline tetramesityldisilene **68**, prepared by West[30] and the *o*-xylylene derivative **69**,[31] the latter being one of a chance observation rather than a product of rational design. Obviously, either electronic or steric or both factors are responsible for the stability of these species. In the case of the transient 10-π electron isobenzofuran,[32] only a handful of stable derivatives are known. The most well-known member of this group is **70** which is commercially available and has found wide use as a trapping agent in Diels-Alder reactions. Another example is **71**.[33] In both **70** and **71** the parent isobenzofuran is obviously stabilized electronically.



67 **68** **69** **70** **71**

Figure 7

In the case of transient furopyridine[5a] **9** no really stable derivative was known. Accordingly, it was of interest to make a stable derivative of this ring system. Padwa *et al*.[34] reported in 1997 that introduction of a carboalkoxy group at the 5-position of the unstable 2-aminofuran stabilizes the system, i.e. **72**. Therefore, it seemed that introduction of a push-pull element, namely an amino group and a carboalkoxy group at appropriate positions in the parent furopyridine **9** would stabilize the system considerably (Figure 8). This turned out to be so in a related dichloro compound, e.g. methyl

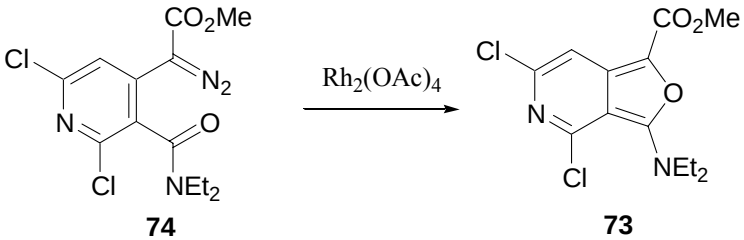


9 **72** **73**

Figure 8

4,6-dichloro-3-(diethylamino)furo[3,4-*c*]pyridine-1-carboxylate (**73**) reported from this laboratory.[35] Thus, when the substituted diazoacetic ester **74** was exposed to 1 mol% $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature for 1h, the furo[3,4-*c*]derivative **73** was obtained in 50% yield as a bright orange air and light-stable crystalline solid, which melted without decomposition at 110-112 ºC (Scheme 7). Compound **73** undergoes

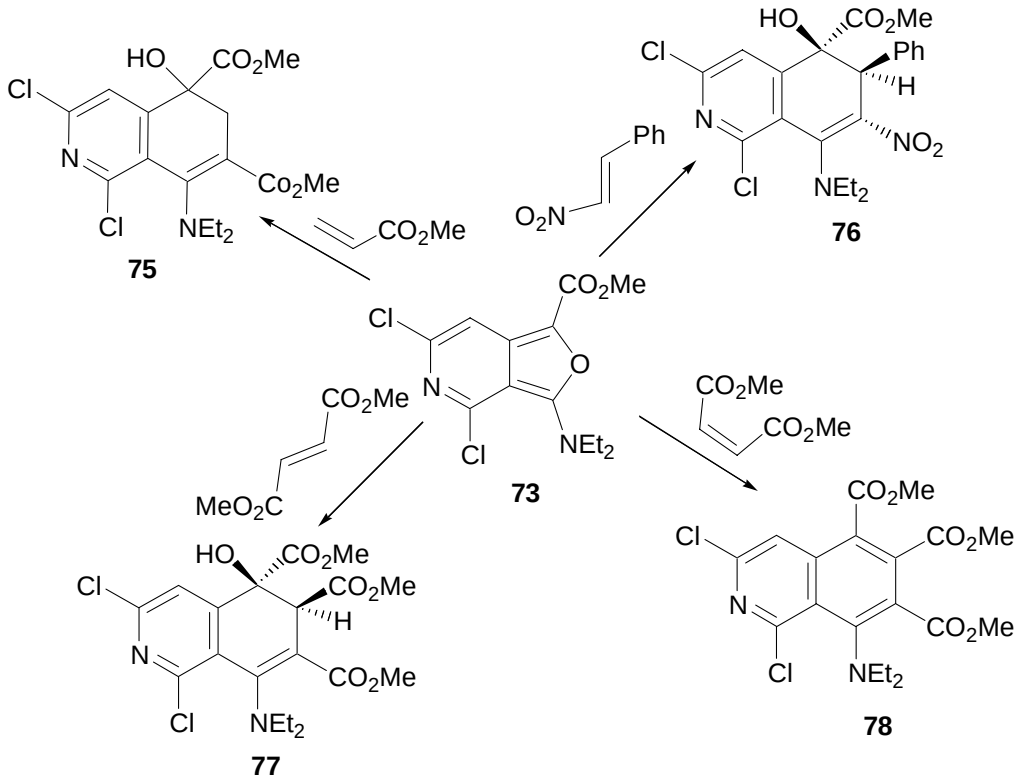
Scheme 7



74 **73**

a facile Diels-Alder cycloaddition with a variety of dienophiles to give polysubstituted isoquinoline derivatives via ring opening of initially formed cycloadducts. In each case the cycloaddition proceeds with high regioselectivity, with the electron withdrawing group located *ortho* to the amino group (Scheme 8).[35b]

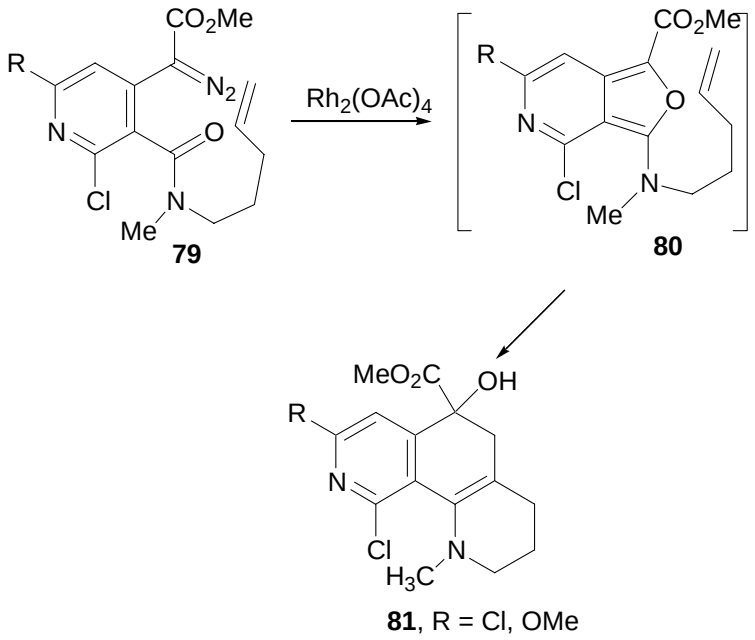
Scheme 8



The first example of an intramolecular Diels-Alder reaction involving a furo[3,4-*c*]pyridine was also reported from this laboratory.[36] For example, exposure of *o*-amidodiazocarbonyl precursors **79** to 1 mol% $Rh_2(OAc)_4$ in refluxing benzene for 1 h gave the bridged anabasine **81** as a yellow crystalline solid formed via intramolecular cycloaddition, followed by ring opening and subsequent proton transfer (Scheme 9).[36a] Thus, a novel route to conformationally restricted anabasines, e. g. **81** with potential as

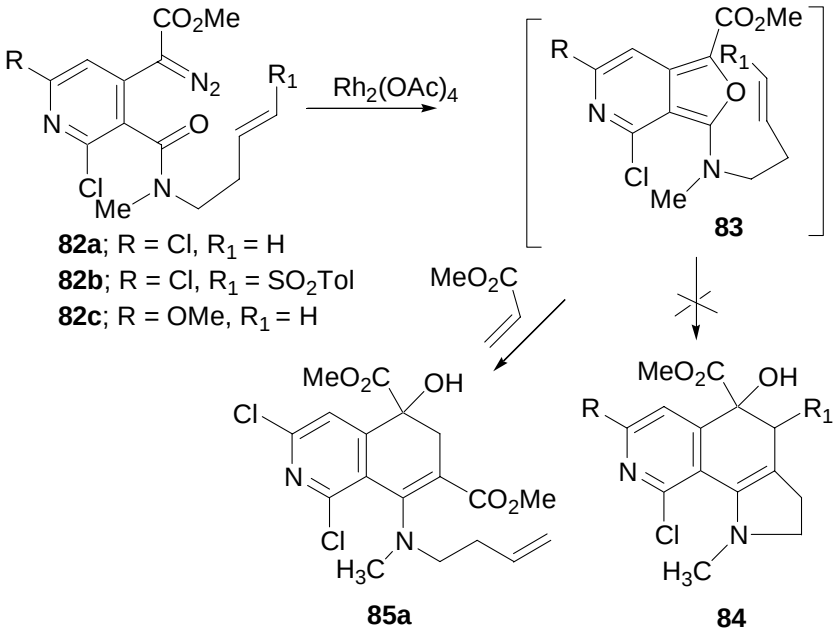
therapeutic agents for central nervous system disease and related disorders was developed.[36b]

Scheme 9



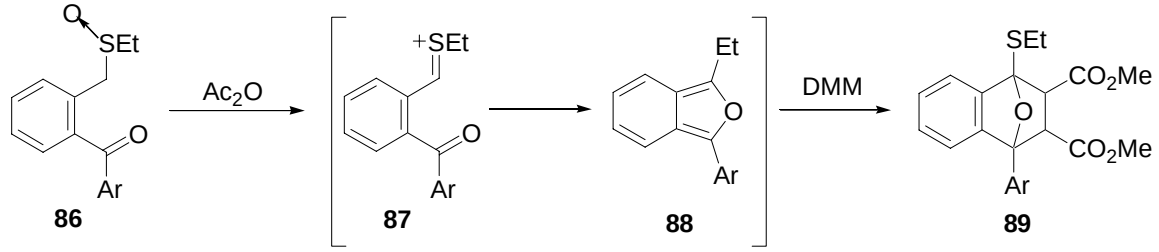
Incidentally, when diazoacetic ester **82a** was subjected to the Rh(II)-catalyzed domino reaction, no intramolecular cycloaddition leading to a bridged nicotine analogue **84** was obtained, even after heating in refluxing benzene for a prolonged time (Scheme 10). However, in this case it was possible to trap the corresponding azaisobenzofuran **83a** with methyl acrylate to furnish cycloadduct **85a**. Unfortunately, even with a built-in activated dienophilic moiety as in **82b** or with an electron-rich diene partner, e.g. **82c**, no domino reaction took place to give the corresponding conformationally constrained nicotine. A detailed density functional theoretical study (B3LYP/6-31+G**) was undertaken to provide insight into the factors that facilitate an intramolecular Diels-Alder reaction in the case of **82a**.[36b]

Scheme 10



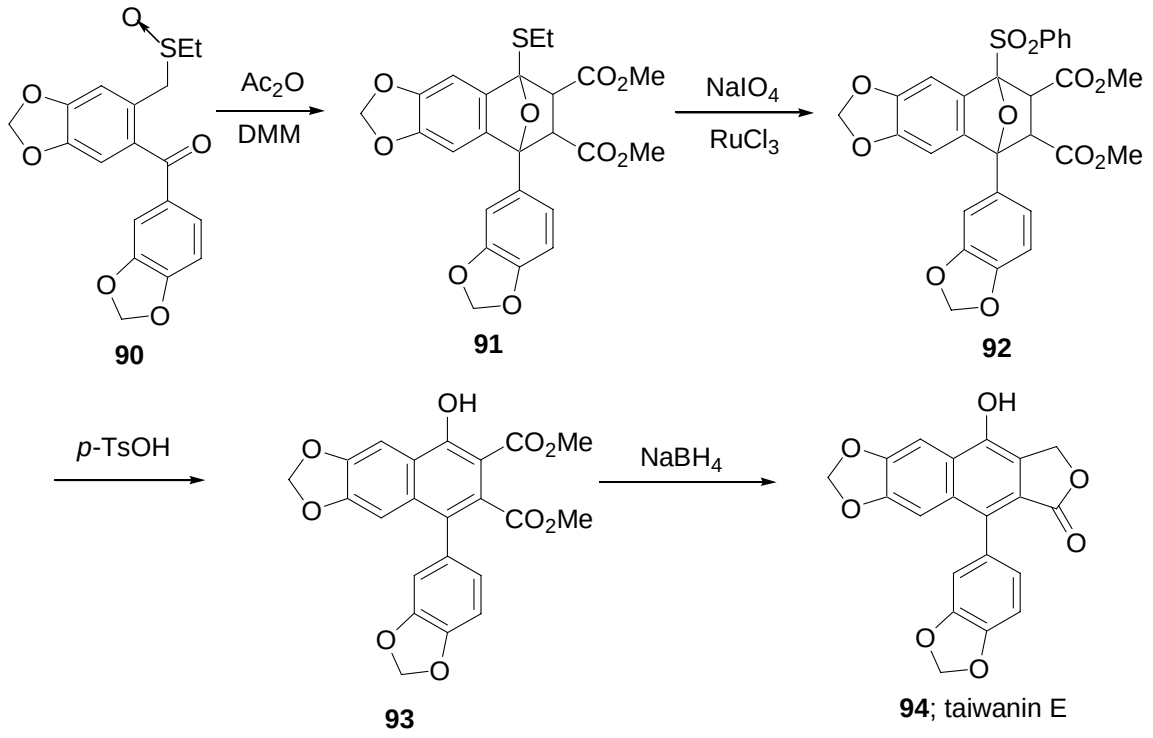
Another piece of work was also undertaken in this laboratory to generate furo[3,4-*c*]pyridines based on the Pummerer route originally developed by Padwa et al.[37] (cf. eq. 6).[10] At this juncture it is deemed important to review Padwa's elegant contribution to the generation and trapping of isobenzofurans and their hetero analogues. Padwa's strategy for the generation of isobenzofurans via the Pummerer route is shown in Scheme 11.[37a] This strategy entails the generation of an α-thiocarbocation and its interception by a neighbouring carbonyl group to give thio-substituted isobenzofuran **88** which undergoes

Scheme 11



Diels-alder reaction to give the cycloadduct **89** (Scheme 11). This methodology worked very well and Padwa et al. showed the utility of the same by synthesizing a number of naturally occurring lignans, such as taiwanin E (**94**).[37a] The synthesis of one such target, e.g. taiwanin E using acetic anhydride as the triggering agent is shown in Scheme 12.

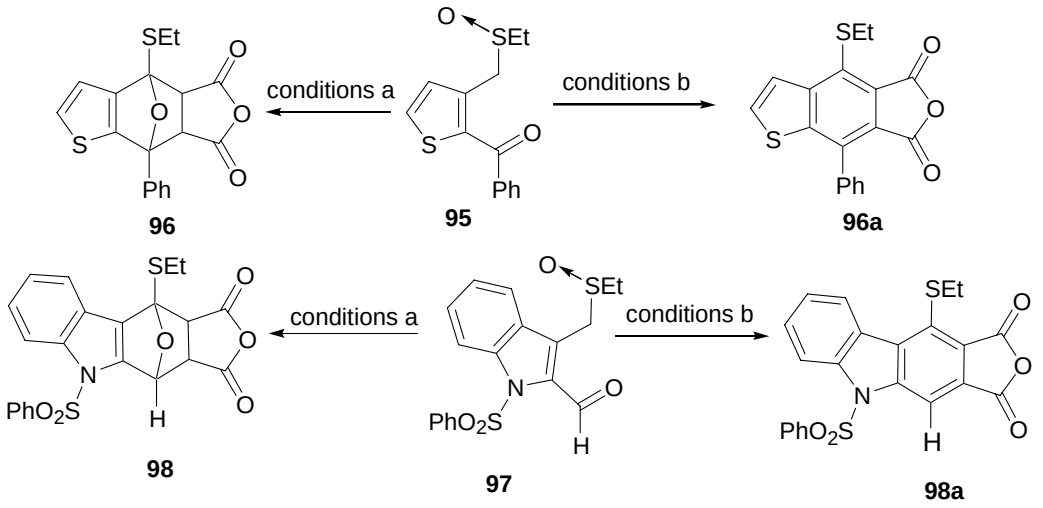
Scheme 12



It is obvious that Padwa et al. would extend this methodology to the synthesis of heteroisobenzofurans.[10] However, when they did they ran into a problem. For example, exposure of **95** and **97** to the same reaction conditions gave Diels-Alder adducts **96** and **98**, but in very poor yield (10-20%);[10] the main byproducts were identified to be compounds of the type **101** (Scheme 14). These results are surprising considering the fact that acetic anhydride is by far the most commonly used reagent and often utilized as the solvent at reflux temperature or in combination with other solvents or cocatalysts.

Two other Pummerer promoters were also employed by Padwa et al. These include the more electrophillic trifluoroacetic anhydride as it allows the reaction to proceed under mild conditions in the presence of basic (e.g. pyridine, triethylamine) or Lewis acid catalysts (e.g. $SnCl_4$) as well as trimethylsilyltrifluromethanesulfonate (TMSOTf) since this reagent permits the reaction to be carried out at temperatures below 0 °C.[38] However, Padwa et al. noted that these conditions were ineffective for forming heteroisobenzofurans and in most cases yielded only the classical Pummerer products of

Scheme 13

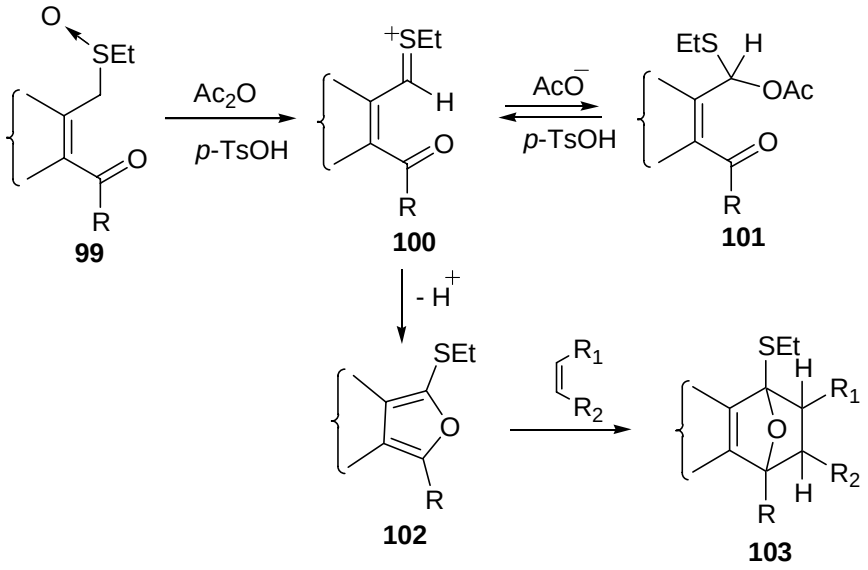


conditions a: Ac_2O, maleic anhydride, toluene, reflux (10-20%)
conditions b: Ac_2O/*p*-TsOH, maleic anhydride, toluene , reflux (80-90%)

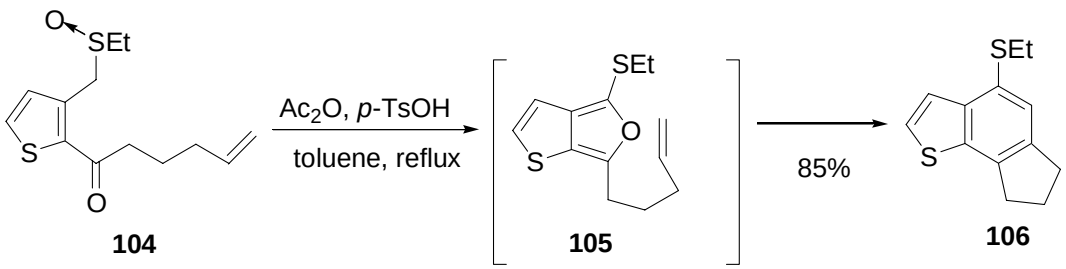
type **101**.[10] In order to improve the yield of the desired heterocyclic cycloadducts, Padwa *et al*. introduced a new condition involving the use of catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) as a cocatalyst with acetic anhydride in refluxing toluene. The presence of *p*-TsOH as a cocatalyst dramatically accelerates the rate of the transformation as compared to reactions carried out without *p*-TsOH.[10] The initially formed thionium ion **100** (Scheme 14) can either be captured internally by the adjacent

carbonyl group to give, after proton loss, the isobenzofuran intermediate **102** or it can react in the traditional sense with an external nucleophile (*i.e.,* AcO^-) to furnish the acetoxy sulfide **101**. The presence of *p*-TsOH effectively drives the reaction in the desired direction (**100→102**) either by preventing the formation of the acetoxy sulfide **101** or by assisting the ejection of the acetoxy group (**101→100**), should **101** be formed; control experiments indeed supported the latter possibility. Under the new condition, **95** and **97** yield **96a** and **98a** in 80% and 90%, respectively (Scheme 13). The new condition was found equally applicable to intramolecular cases (Scheme 15).[10]

Scheme 14

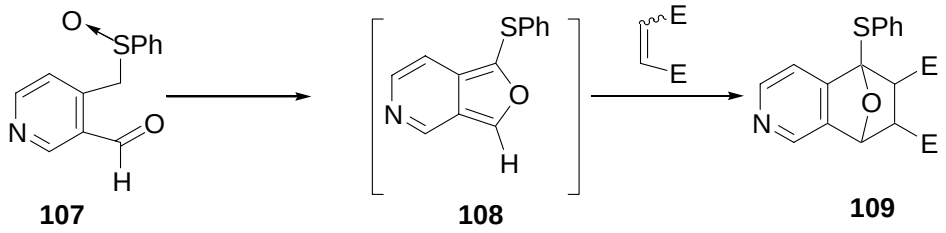


Scheme 15



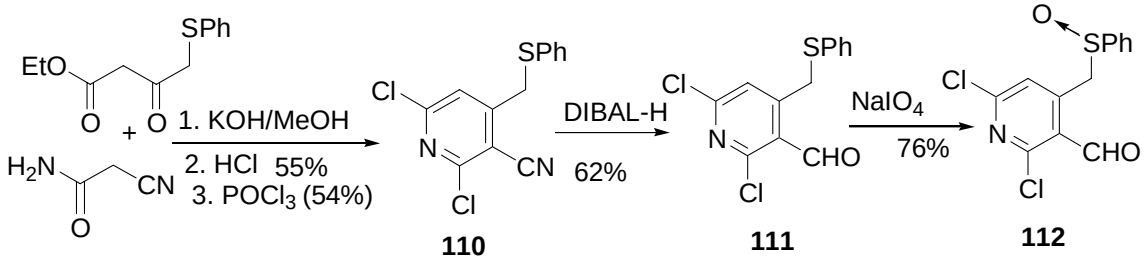
Inspired by the pioneering work of Padwa et. al. Sarkar et. al. initiated work on generation and trapping of furo[3,4-*c*]pyridines as depicted in Scheme 16.

Scheme 16



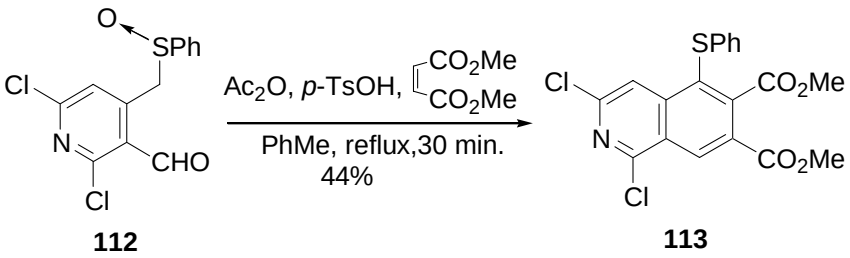
To test the feasibility of this idea a simple sulfoxide precursor **112** was made from nitrile **110** by Dr. S. Basak from this laboratory (Scheme 17). Dr. Basak found that when

Scheme 17



112 was treated with a suitable dienophile e.g. dimethyl maleate under standard Pummerer reaction conditions (Ac_2O/ *p*-TsOH, toluene, reflux) developed by Padwa *et al.*[10] **113** was formed in 44% yield as a white crystalline solid (mp 109-111°C) (Scheme 18). In this case, the [4+2]-adduct (*cf.* **109**) underwent spontaneous ring cleavage followed by dehydration.

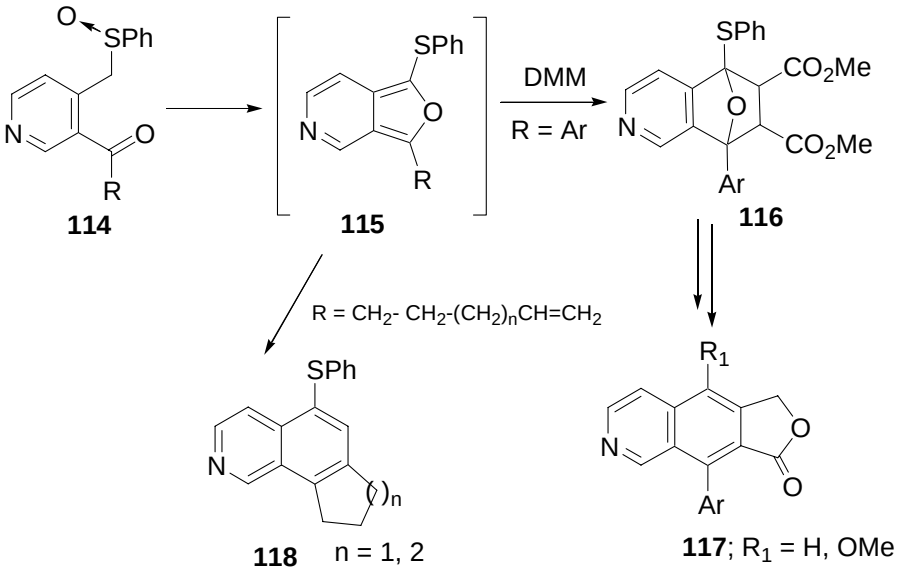
Scheme 18



3. Present work

The foregoing encouraging results on the generation and trapping of furo[3,4-*c*]pyridine prompted us to study the scope and limitations of this work. Along this line it was decided to study tandem Pummerer-Diels-Alder reaction on keto-sulfoxide e.g. **114** (Scheme 19) where R stands for either aryl or alkenyl groups. While with the former, one could get hold of heterolignans e.g. **117**, the latter was chosen to test the applicability of the Scheme in intramolecular cases leading to tricyclic systems, e.g. **118**. Admittedly, the proposed heterolignan synthesis is part of a curiosity drive rather than addressing current challenges described in Section 1.2.

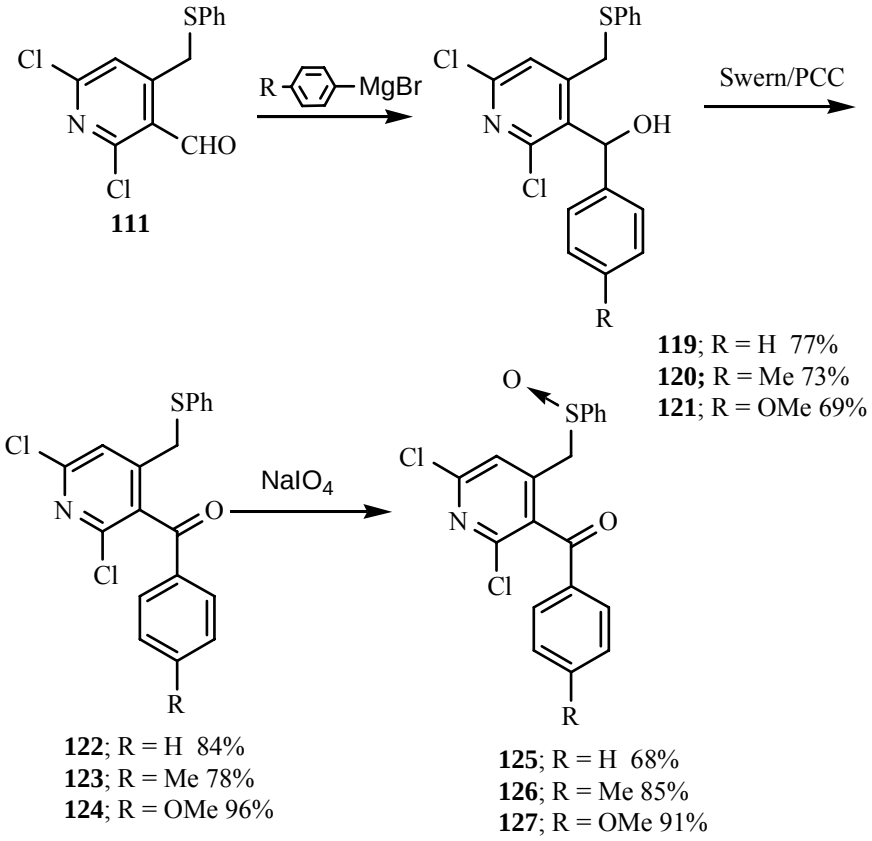
Scheme 19



4. Results and Discussion

Our study started from the thio-substituted nicotinaldehyde **111** which on treatment with aryl Grignard reagents in THF at -78 °C gave the corresponding alcohol (**119**-**121**) (Scheme 20) in good yield. The formation of **119**-**121** was evident from

Scheme 20



spectral data. For example, the presence of molecular ion peak at m/z 390 ($[M+H]^+$, $C_{20}H_{18}Cl_2NOS$) in mass spectrum and appearance of absorption band at 3371 cm^{-1} due to O-H group with disappearance of the absorption band at 1688 cm^{-1} for aldehyde **111** in IR reveals the formation of alcohol **120**. In ^1H NMR the presence of a singlet at 2.36 for $CH_3C_6H_4$ and doublets at 3.84 and 4.26 with J = 15.3 Hz indicated the *AB* system for CH_2SPh protons in **120**. The structure of alcohol **120** was further confirmed from 16 line

signals in ^{13}C NMR as well as HRMS data. Alcohols **119** and **120** undergo clean oxidation to ketones **122** and **123**, respectively under Swern oxidation condition. It can be mentioned here that alcohol **121** does not undergo oxidation under the same condition; rather a mixture of decomposition products (TLC) were formed which were not further characterized. The decomposition products might include some chlorinated compounds and indeed there is precedent in indole chemistry that chlorination competes over oxidation.[39] The formation of such products may be explained in terms of the involvement of oxygen lone pair towards the formation of unstable intermediate **128a**, which undergoes rapid decomposition under the reaction conditions (Figure 9). Later it

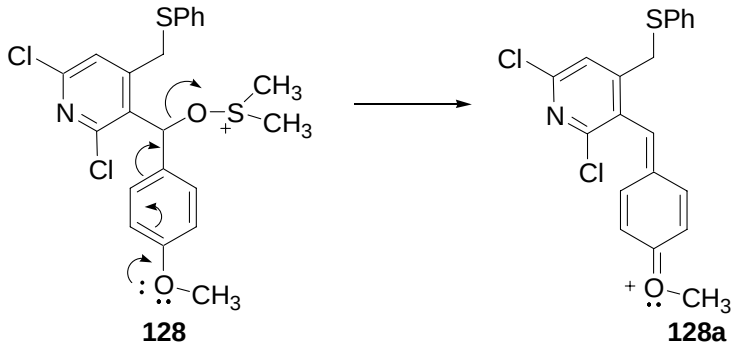


Figure 9

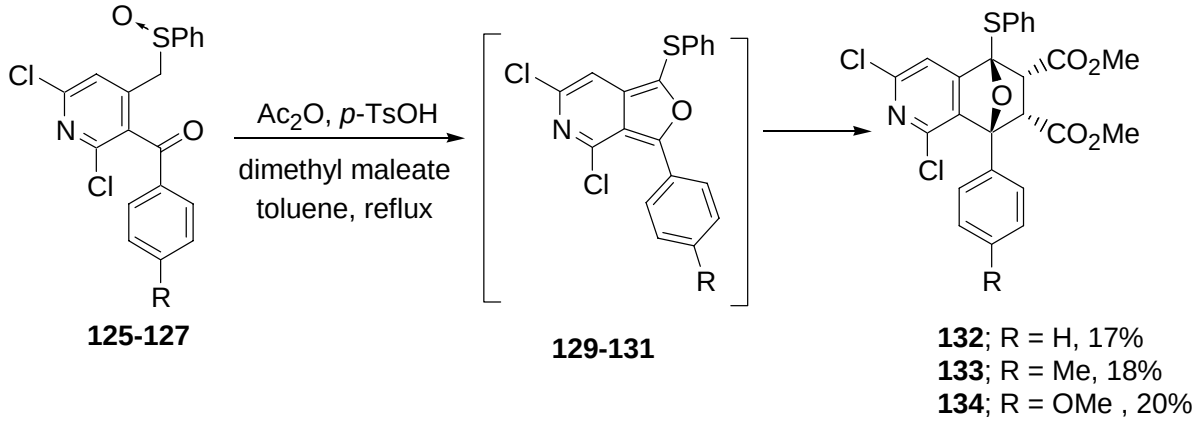
was found that the alcohol **121** could be converted to the corresponding ketone **124** by PCC at room temperature in CH_2Cl_2 in excellent yield. The structure of **124** was fully supported by spectral data. The precursors for the sequential Diels-Alder reaction, namely the sulfoxides **125**–**127** were synthesized from the corresponding sulfides **122**–**124** by oxidation with $NaIO_4$ in methanol-water. The structures of sulfoxides **125**–**127** were evident from spectral data. For example, in ^1H NMR of **126** there is disappearance of a singlet at δ 3.90 for two protons of C*H*$_2$SPh and appearance of doublets at 3.79 and

3.92 with J = 12.8 Hz indicating the *AB* system for CH_2SOPh. Presence of molecular ion peak at m/z 421 ($[M+NH_4]^+$, $C_{20}H_{19}Cl_2N_2OS$) in DCI-MS and appearance of absorption band at 1668 cm^{-1} due to carbonyl group, 1327 and 1085 cm^{-1} due to sulfoxide group in IR also support the structure of **126**. Finally ^{13}C NMR (16 lines) and HRMS data confirmed the structure of **126**. The main drawback in the $NaIO_4$-mediated oxidation of sulfides **122**–**124** is long reaction time, i.e. 15 – 20 days are required to obtain sulfoxides in acceptable yields. For rapid access to these sulfoxides we subsequently found that treatment of keto-sulfides to excess amount of peracetic acid is the method of choice. For example, treatment of **123** with peracetic acid (32 wt %) in ether under refluxing condition for 30 minutes gave 70% of the keto-sulfoxide **126** and remaining starting material which can be recovered.

With the keto-sulfoxide **125-127** in hand, we turned our attention to the formation of some azalignans via the standard sequential Pummerer-Diels-Alder reaction condition. Thus, treatment of keto-sulfoxide **125** with acetic anhydride, *p*-toluenesulfonic acid in presence of dimethyl maleate in refluxing toluene gave the bridged product **132**, albeit in 17% yield only (Scheme 21). The structure of **132** was assigned from ^1H NMR showing characteristic signals at δ 3.57 as singlet for ester protons (CO_2CH_3), and doublets at 3.61 and 4.16 for C*H* protons with coupling constant 11.2 Hz. Additionally, the presence of two quaternary carbon signals at δ 167.6, 168.9 due to two *C*$OOCH_3$, methyl carbon signals at δ 51.9 and 52.5 due to COO*C*H_3 along with other 17 lines in ^{13}C NMR confirms the structure of **132**. The stereochemistry of **132** is tentatively assigned on the basis of Alder endo rule. Similarly, when keto-sulfoxides **126** and **127** were subjected to the same conditions **133** and **134** were obtained in only 18 and 20% yields, respectively.

The formation of the endo-adduct was confirmed from single crystal X-ray structure determination of **134**. The X-ray work was carried out by Professor H. –K. Fun (Malaysia) and the ORTEP diagram is shown in Figure 10.

Scheme 21



125-127

129-131

132; R = H, 17%
133; R = Me, 18%
134; R = OMe , 20%

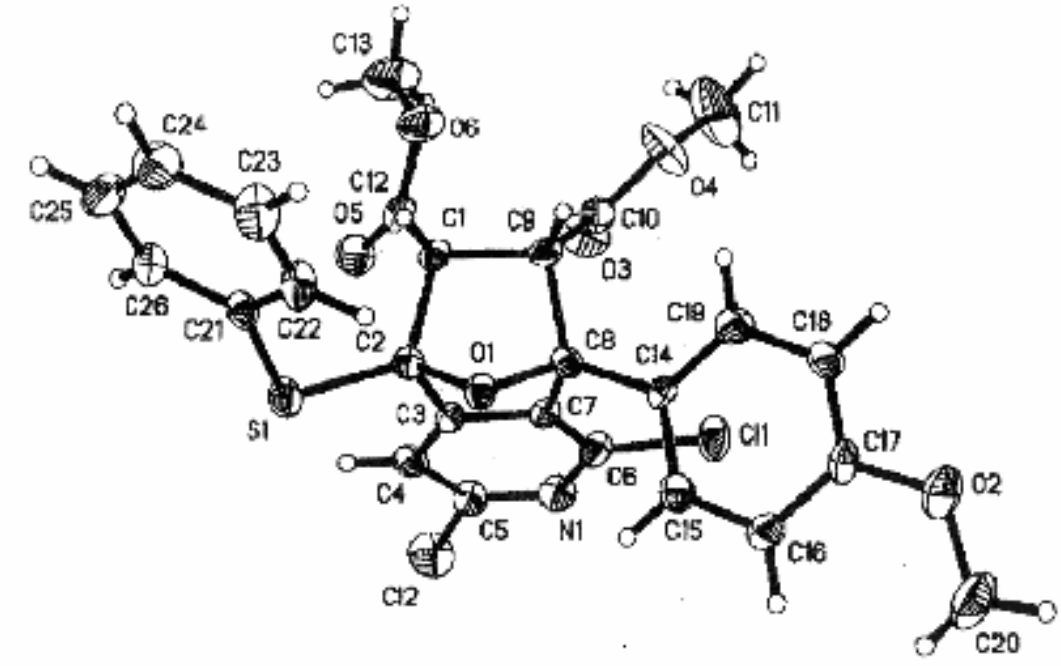


Figure 10. ORTEP diagram of **134**

The low yield of the cycloadducts **132-134** was due to the formation of Pummerer classical products, *e.g*. acetoxy sulfides of type **135** as major products along with miscellaneous other side products, which were not further investigated (Figure 11). For example, in the Pummerer reaction of **127,** the acetoxy sulfide **136** was isolated as a white crystalline compound. Structure of **135** was evident from spectral data. Presence of absorption band at 1763 cm^{-1} due to acetate carbonyl group and 1661 cm^{-1} due to the other carbonyl group in IR reveals the formation of the acetate product. In ^{1}H NMR the

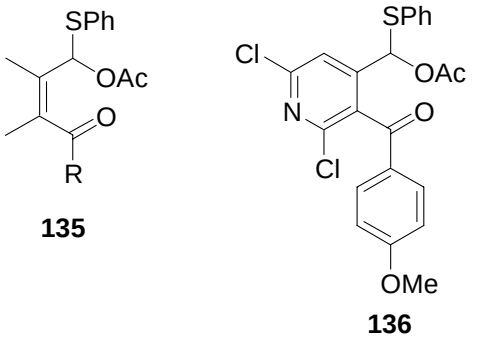
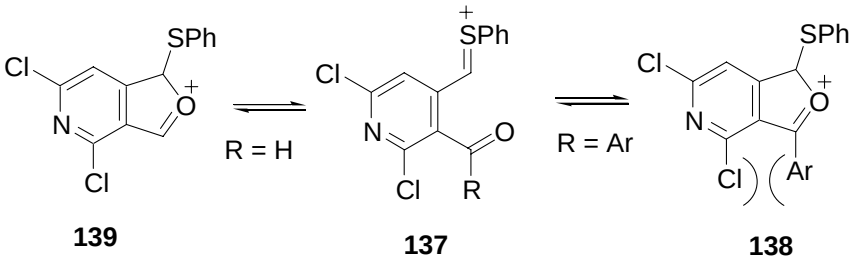


Figure 11

singlets at δ 1.98 due to the acetate protons and 3.88 due to the methoxy protons support the structure of **136**. Furthermore, the presence of $OCOCH_3$ group in **136** was also evident from LCMS which shows *m/z* (relative intensity) at 462 ($[M + H]^+$, 8), 402 ($[M – OAc]^+$, 100), 292 ($[M – OAc -PhSH]^+$, 71). The structure of **136** is further confirmed from the appearance of a methine carbon signal at δ 77.4 (due to *C*H(SPh)OAc) along with other 17 lines in ^{13}C NMR spectrum. In order to improve the yield of the reaction, the keto-sulfoxide **124** was treated with other known Pummerer conditions (e.g. acetic anhydride, reflux; acetic anhydride/$BF_3.Et_2O$, reflux; trifluoracetic anhydride/ Et_3N at 0 °C; trifluoroacetic anhydride/*p*-TsOH) in presence of dimethyl maleate). But surprisingly

none of these conditions were suitable for yield improvement. At this stage we wondered as to why the yield of cycloadducts in all three cases (Scheme 21) is poorer in comparison with the formation of **113** from **112** (Scheme 18). This may be due to the steric effect which disfavours the formation of **138** from **137** (Scheme 22) when compared with the formation of **139**. Therefore, in the presence of stronger nucleophiles like acetate ion, **137** leads to compounds of the type **135**. This suggests that if very poor nucleophiles are present in the medium, species such as **137** will not be trapped and any **138** formed will undergo elimination of proton to generate the azaisobenzofuran intermediate (cf. **115**, Scheme 19) leading to the desired cycloadducts. This prompted us

Scheme 22

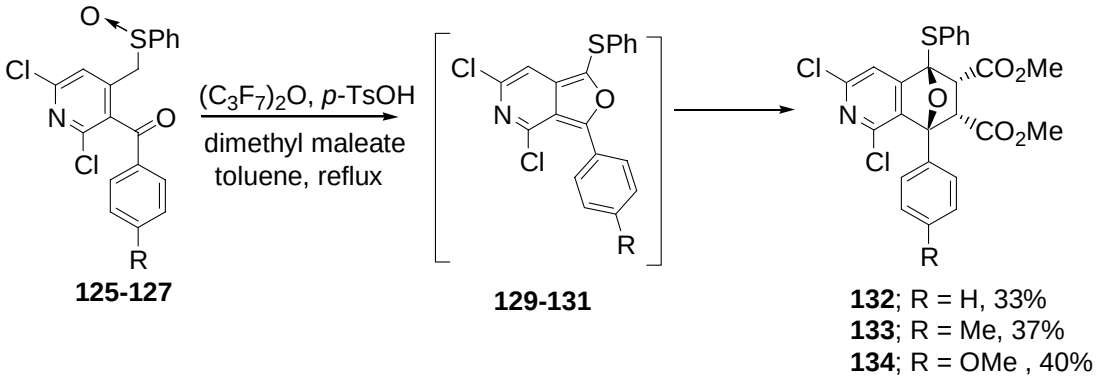


139 **137** **138**

to develop a modified triggering agent in order to achieve acceptable yields of desired bridged cycloadducts and heptafluorobutyric anhydride was found to be a better triggering agent than acetic anhydride/*p*-TsOH (Padwa's condition[10]). Under this modified protocol, keto-sulfoxides **125**–**127** smoothly gave the bridged cycloadducts **132**–**134** with improved yields as shown in Scheme 23. Obviously, this improvement is either due to the poorer nucleophilicity of 'counterion' ($C_3F_7CO_2^-$) towards Pummerer intermediate (cf. **137**) generated in the reaction medium, thereby preventing the

formation of sulfides of type **135** or, due to better leaving group ability of the same 'counterion' from species, e.g. **135**.

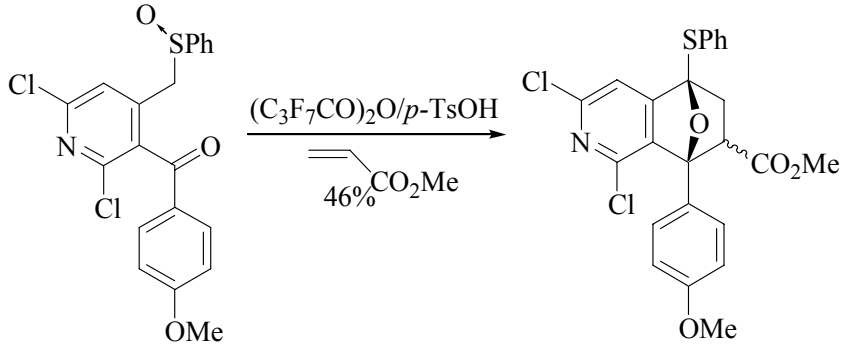
Scheme 23



In order to study the stability of the transient intermediates, that is the thio substituted furo[3,4-*c*]pyridines **129-131**, the keto-sulfoxide **127** was treated with the triggering agent, heptafluorobutyric anhydride/ *p*-toluenesulfonic acid in the absence of a dienophile under reflux condition in toluene. This time we were able to isolate the intermediate α-thiosubstituted furo[3,4-*c*]pyridine **131** as a yellow oil by rapid flash chromatography. We found that **131** is quite unstable and undergoes aerial decomposition attended with disappearance of color in a few hours. However, the intermediate could be characterized by ^{1}H NMR spectroscopy showing characteristic singlets at δ 3.88 and 7.31 for OCH_3 group and the pyridine proton, respectively with disappearance of doublets at 3.73 and 3.87 for CH_2SOPh in **127**. The absence of the absorption band at 1687 cm^{-1} for carbonyl group in IR is also supportive of the structure. Furthermore, when **131** was exposed to dimethylmaleate in toluene under reflux, **134** was formed in low yield. It may be noted that azaisobenzofuran **131** also undergoes Diels-Alder reaction with less reactive dienophiles. Thus, exposure of **131** to the

Pummerer-Diels-Alder reaction protocol in presence of methyl acrylate as dienophile gave cycloadducts **140** and **141** as a 4:1 mixture as evident from the relative intensity of the COO*Me* signals in ^{1}H NMR (Scheme 24). It may be mentioned here that the major product **140** was isolated as white crystals by crystallization of the mixture from 5% ethyl acetate:petroleum ether.

Scheme 24



127

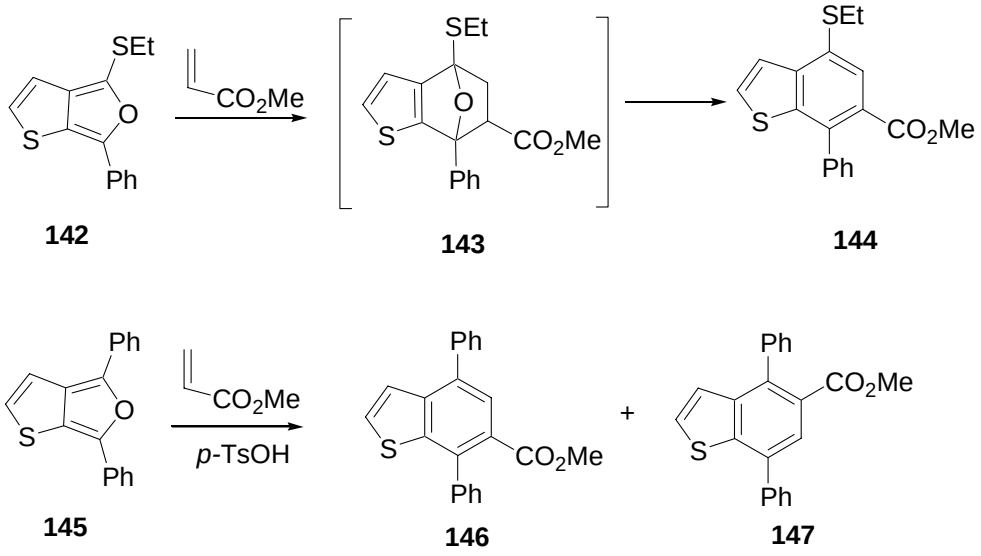
140; α-CO_2Me

141; β-CO_2Me

The formation of the bridged adduct was evident from spectral data. The ^{1}H NMR spectrum of **140** shows a typical *ABC* pattern of splitting at δ 2.12 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.2 Hz), 2.58 (dd, 1H, J_1 = 12.2 Hz, J_2 = 10.2 Hz) for CH_2 protons and 3.91 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.2 Hz) for C*H*CO_2Me. In ^{13}C NMR the appearance of methine carbon signal at δ 47.7 due to *C*HCO_2Me and methyl carbon signal at 52.4 due to CHCO_2*Me* along with other 17 signals confirm the formation of cycloadduct **140**. The stereochemical assignment for **140** was confirmed from single crystal X-ray crystallography.[40] The ORTEP diagram and crystal packing of **140** is presented in Figures 12 and 13, respectively. The structure of minor product is tentatively assigned as **141** (Scheme 24). It is appropriate to mention here that Padwa *et al.*[10] reported that treatment of ethyl thio-substituted thieno[2,3-*c*]furan **142** with methyl acrylate in

presence of $Sc(OTf)_3$ gave the only regio isomer **143** which undergoes instantaneous dehydration to give the fully aromatized product **144** (Scheme 25). They mentioned that the ethylthio group plays an important role in terms of influencing the regiochemistry of Diels-Alder reaction. It may be noted that in the work of Friedrichsen et al.[41] the Diels-Alder reaction of 4,6-diphenyl thieno[2,3-*c*]furan **145** with methyl acrylate followed by dehydration produce 1:1 regioisomeric cycloadducts **146** and **147**. Padwa et al. reported that the formation of adduct **144** as a single regioisomer is consistent with FMO theory. The most favorable interaction is between the HOMO of the thieno[2,3-*c*]furan and LUMO of methyl acrylate. The atomic coefficient at the ethylthio-substituted position in furan ring is larger than at the phenyl position in the HOMO and this nicely accommodates the high regioselectivity encountered.

Scheme 25



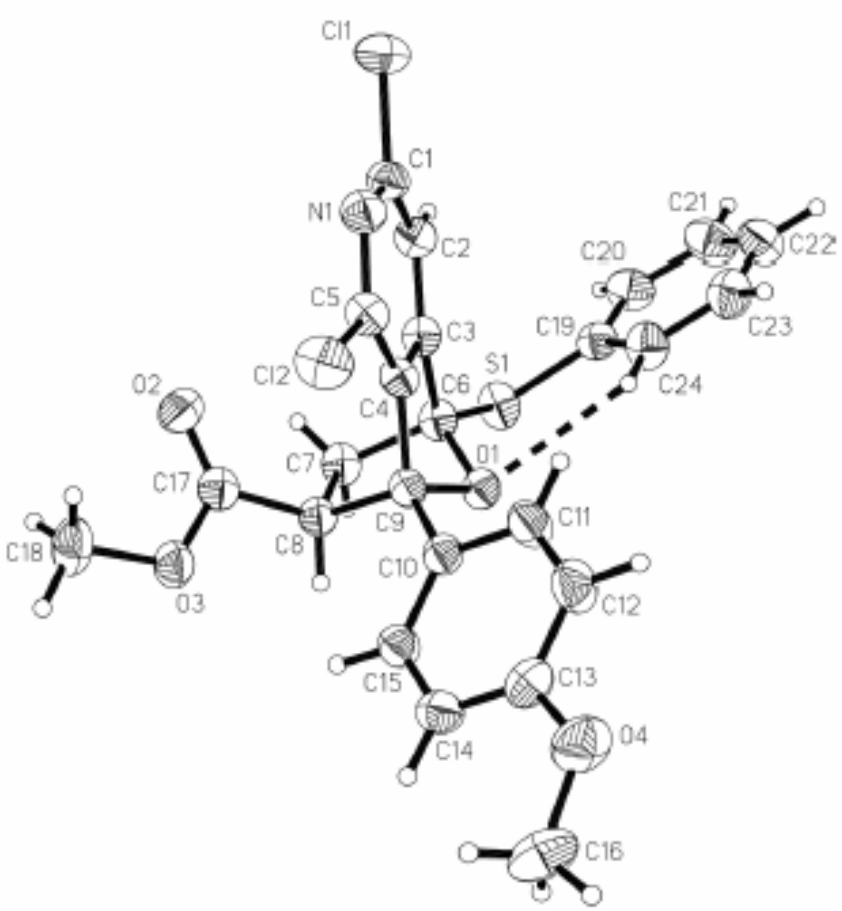


Figure 12. ORTEP diagram of **140**

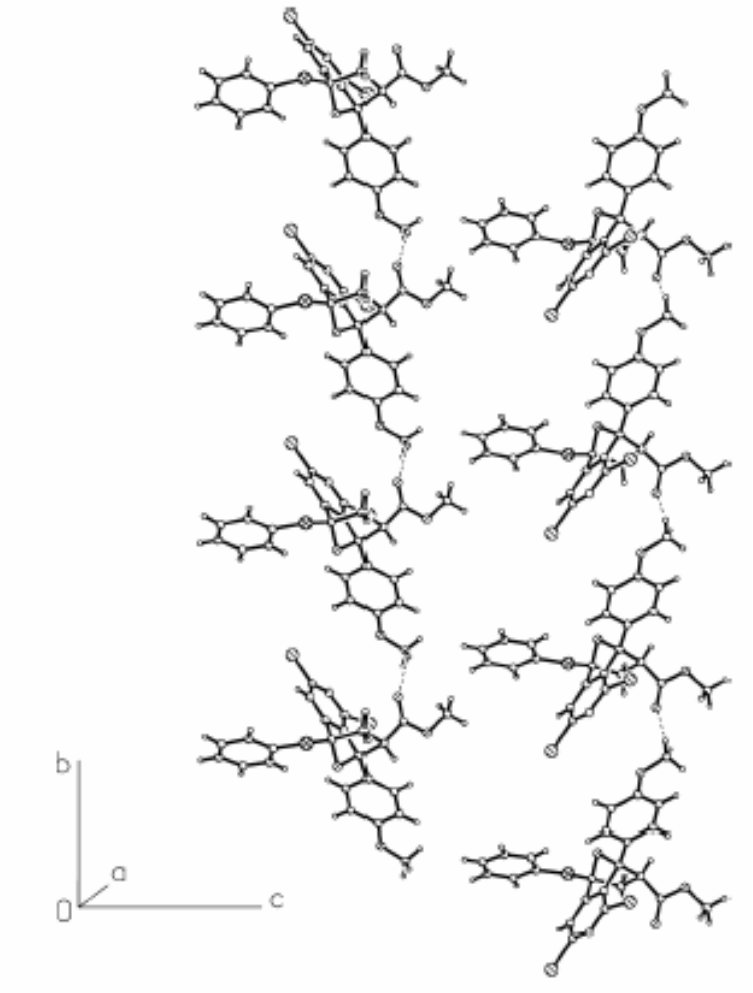


Figure 13. Crystal packing diagram of **140**

In our case the regio- and stereoselectivity in the cycloaddition of **131** with methyl acrylate may also be rationalized by FMO theory.[42] The orbital co-efficients as well as energy difference between the HOMO of **131** and LUMO of methyl acrylate (MA) were determined by restricted Hartree-Fock ab-initio calculations using GAMESS quantum chemistry package.[43] The calculations were carried out using two basis sets with Gaussian basis set i.e. Slater-type orbitals (STO 3-21G* and STO 6-31G**) for comparison. In fact, Firoj Jaipuri (USA) did the calculation with GAMESS HF/3-21 G*

initially and later the results were verified using the other basis sets by Sajeev Yasoodharan (Technion, Israel Institute of Technology, Israel) (Table 1). It has been concluded that the atomic coefficient of the phenylthio-substituted carbon in the heteroisobenzofuran ring is larger than the anisyl substituted carbon in the HOMO of **131.** This matches with the bigger atomic coefficient of CH_2 carbon and smaller CH carbon of methyl acrylate (MA) respectively in LUMO to accommodate the regioselective product **140** from the Diels-Alder reaction.

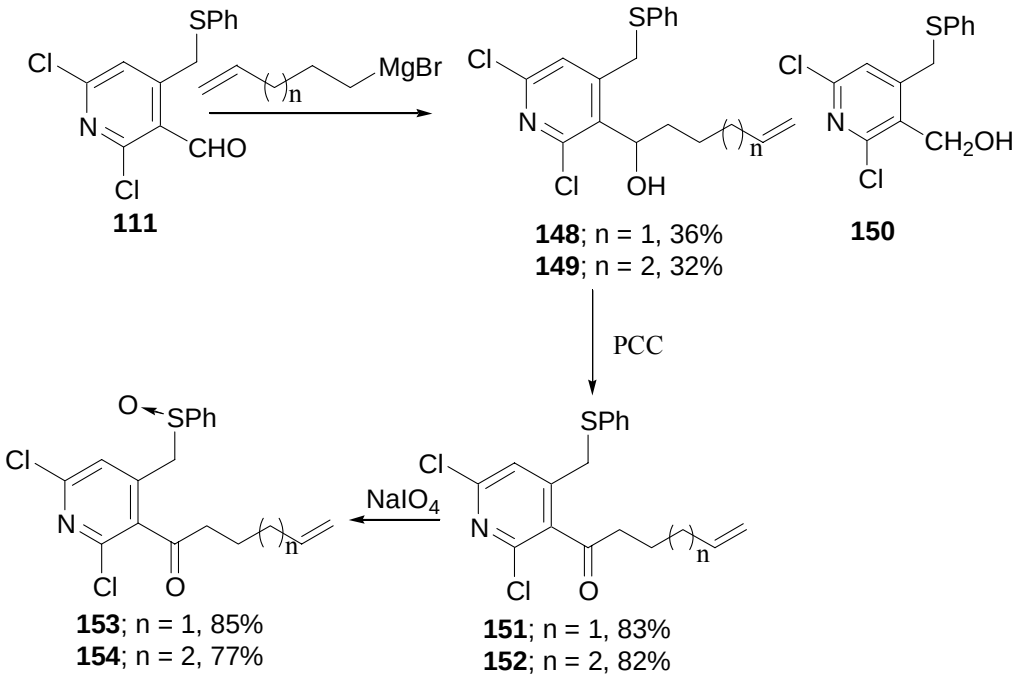
Table 1

GAMESS/ Basis sets	Energy Difference : LUMO of MA and HOMO of **131**	Orbital co-efficient of SPh substituted C of **131**	Orbital co-efficient of anisyl substituted C of **131**	Orbital co-efficient of CH_2 (terminal) C of MA	Orbital co-efficient of CO_2Me substituted CH of MA
HF/ 3-21G*	4.8 ev	0.314	0.23	0.63	0.464
HF/6-31G**	10.13 ev	0.481	0.420	0.930	0.688

The Pummerer-based route for the generation and trapping of α-thiosubstituted furo[3,4-*c*]pyridines can also be extended to intramolecular cases. The precursors for intramolecular Diels-Alder reaction, that is tethered sulfoxides **153** and **154** were prepared in a similar fashion as described in Scheme 20. Treatment of the thio-substituted nicotinaldehyde **111** with alkenyl Grignard reagents at -78 °C in THF gave the corresponding alcohols **148** and **149**, respectively in 32-36% yield (Scheme 26), which were characterized by ^{1}H as well as ^{13} C NMR. Here, the poor yield of the alcohol is due

to the formation of (2,6-dichloro-4-((phenylthio)methyl)pyridine-3-yl)methanol (**150**) as a byproduct. The structure of **150** is confirmed from its spectral data. Presence of

Scheme 26

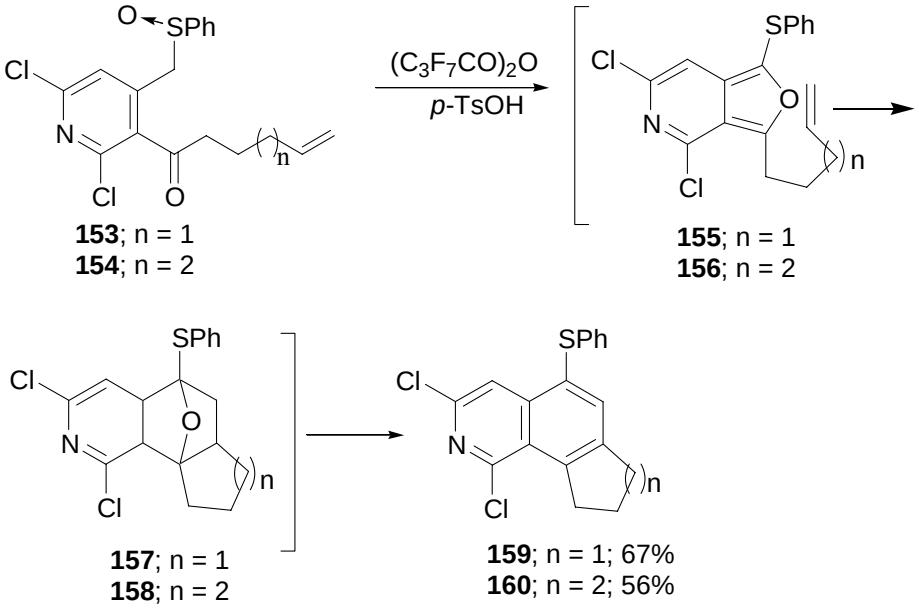


molecular ion peak at *m/z* 300 ($[M+H]^+$, $C_{13}H_{12}Cl_2NOS$) in the mass spectrum revealed the formation of **150**. In ^1H NMR two singlets at δ 4.12 and 4.76 for two methylene protons and another singlet at 6.89 for the pyridine proton established the structure of alcohol **150**, which was further confirmed by 11 lines in the ^{13}C NMR spectrum. The yield of **148/149** could have been improved if the alkenyl Grignard reagents were replaced by the corresponding lithiated reagents; however, this was not done. The alcohols **148** and **149** undergo clean oxidation to the corresponding ketones **151** and **152** by PCC in CH_2Cl_2. The formation of ketones **151** and **152** was evident from spectral data. For example, the presence of molecular ion peak at *m/z* 383 ($[M+NH_4]^+$, $C_{18}H_{21}Cl_2N_2OS$) in the mass spectrum and presence of absorption band at 1707 cm^{-1} in

IR spectra reveals the formation of ketone **151**. In ^{13}C NMR the disappearance of the methine carbon signal (*C*HOH) at δ 71.1 and appearance of quaternary carbon signal at 202.7 for *C*O established the formation of ketone **151**. The keto-sulfides on treatment with $NaIO_4$ for 3-4 days in methanol-water gave the keto-sulfoxides **153** and **154**. Formation of keto-sulfoxides **153** and **154** was evident from spectral data. Presence of absorption band at 1702 cm^{-1} for carbonyl group in IR spectra and the appearance of doublets at δ 3.71 and 4.12 (J = 12.9 Hz, *AB* system) for CH_2SOPh in ^1H NMR proves the formation of sulfoxide **153**.

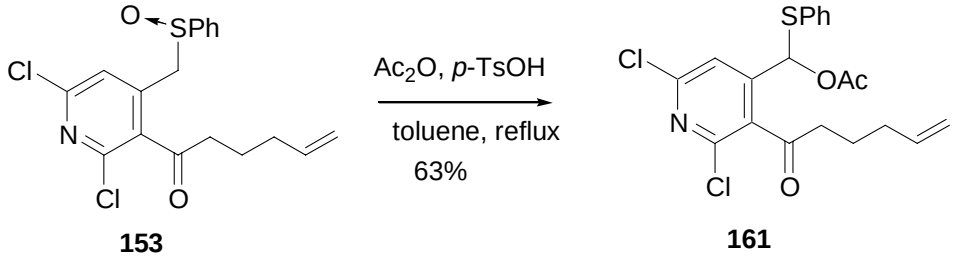
Subjection of **153** and **154** to the modified Pummerer conditions (heptafluorobutyric anhydride/*p*-TsOH) led to polycyclic ring systems **159** and **160**, respectively in one pot with good yields (Scheme 27). Structures of **159** and **160** were fully established by spectral data. For example, in ^1H NMR of **159**, the presence of clean triplets at δ 3.03 (J = 7.7 Hz) and 3.74 (J = 7.5 Hz) and disappearance of the multiplets for terminal double bond at 5.05 and 5.50 along with appearance of two singlets at 7.78 and 8.20 for two aromatic protons provides evidence for the formation of tricyclic compound **159**. Furthermore, in ^{13}C NMR disappearance of the quaternary carbon signal (*C*O) of **153** at δ 203.3 and presence of only three triplet carbon signals at 24.3, 33.3 and 36.4 for three methylene carbons along with other 13 lines proves the structure. The need for our new triggering agent for initiating the Pummerer reaction is best exemplified in these intramolecular series. For example, when keto-sulfoxide **153** was subjected to the other Pummerer condition, i.e. refluxing with Ac_2O in presence of *p-TsOH*[10] *no trace of product resulting from an intramolecular Diels-Alder reaction could be detected in the*

Scheme 27



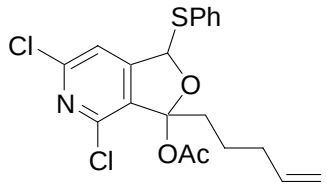
*crude reaction mixture by TLC; rather the acetoxy product **161** was* formed in 63% yield (Scheme 28). The structure of **161** is settled on the basis of spectral data, especially after comparing the spectral data with our previous acetoxy byproduct i.e. **136** as well as **151**

Scheme 28



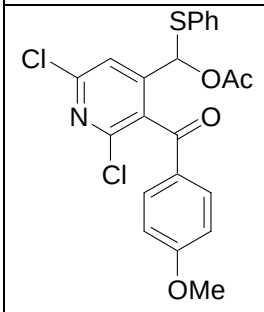
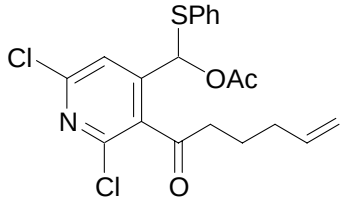
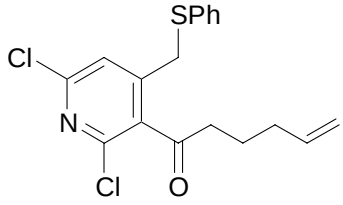
(Table 2). In IR the presence of absorption bands at 1756 cm^{-1} is due to the acetoxy carbonyl group and the one at 1701 cm^{-1} due to the other carbonyl group. The molecular composition of **161** was evident from HRMS data (*m/z* 424.0542, $[M+H]^+$,

$C_{20}H_{20}Cl_2NO_3S$). The ^{1}H- NMR of **161** shows characteristic singlets at δ 2.12 and 6.85 for (OCOC*H*$_3$) and C*H*(SPh)OAc, respectively with disappearance of the doublets at 3.71 and 4.12 for C*H*$_2$(SOPh) in **153**. The presence of the signals for the olefinic protons as well as for the aliphatic C*H*$_2$ groups proves the presence of a dangling aliphatic chain with a terminal double bond. In ^{13}C NMR, the presence of quaternary carbon signals at δ 202.3 and 168.9 is due to *C*OCH$_2$CH$_2$ and O*C*OCH$_3$ respectively; note that the disappearance of the signal for *C*H$_2$(SOPh) at 59.0 and appearance of methine carbon signal for *C*H(OCOCH$_3$) at 76.5 and methyl carbon signal CH(OCO*C*H$_3$) at 20.9 *rule out the possibility of any other structure such as the cyclic product **162***. Furthermore, if **162** was the product, one would expect it to form as a mixture of two diastereomers, not one; *the ^{13}C NMR of **161** shows that it is a single compound.* One question that may be raised at this point is why this molecule i.e., **161** does not fragment in refluxing toluene. This may be due to the poor leaving group ability of the acetoxy group. Besides, such byproducts (cf. **101**) have been reported by Padwa[10] under similar conditions. Incidentally, **161** is a robust molecule and it does not decompose to the corresponding aldehyde. The high-yielding intramolecular [4+2]-cycloaddition reaction of **155** and **156** is obviously related to entropic factors which place the tethered double bond in close proximity to the diene system.



162

Table 2

Compounds	IR	^{1}H NMR	^{13}C NMR
 **136**	1763 cm^{-1} for O*CO*CH_3 1661 cm^{-1} for *CO*Ar	7.16 ppm (C*H*(SPh)OAc)	189.9 ppm (*C*OAr) 168.3 ppm (O*C*OCH_3) 77.4 ppm (*C*H(SPh)OAc)
 **161**	1756 cm^{-1} for O*CO*CH_3 1701 cm^{-1} for *CO*CH_2-	6.85 ppm (C*H*(SPh)OAc)	202.3 ppm (*CO*CH_2-) 168.7 ppm (O*C*OCH_3) 76.5 ppm (*C*H(SPh)OAc)
 **151**	1707 cm^{-1} for *CO*CH_2-		202.7 ppm (*CO*CH_2-)

Appropriately functionalized polycyclic aromatic compounds have anti-tumor activity by virtue of their ability to intercalate between adjacent heterocyclic bases of DNA.[44] By contrast, non-planar precursors to such molecules are likely to exhibit low affinity for DNA. Chemical insight allowed us to consider azaisobenzofuran-derived

Diels-Alder adducts **132-134** as low cytotoxicity precursors, 'prodrugs,' of intercalating agents. The activation of such adducts selectively at a tumour site might form the basis of anti-cancer chemotherapies with reduced side effects. Prodrug activation strategies have been pursued with increasing vigour in recent years.[45] Since thiol groups can be released from appropriately substituted precursors at tumors, namely by bioreduction[46] or by antibody-directed enzyme catalysis[47] azaisobenzofuran Diels-Alder adducts e.g. **132-134** with bridgehead sulfide groups maybe looked upon as potential antitumour prodrugs where cleavage of a sulfide linkage can lead to aromatization of the oxanorbornyl ring system [48] (Figure 14).

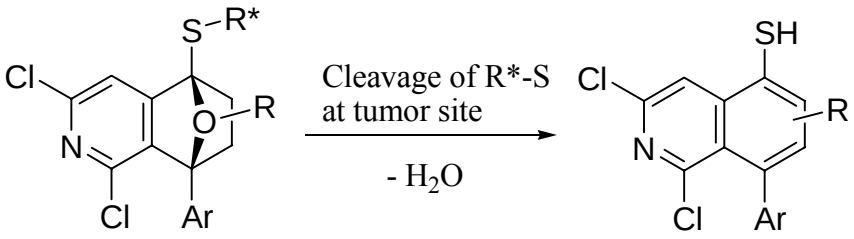
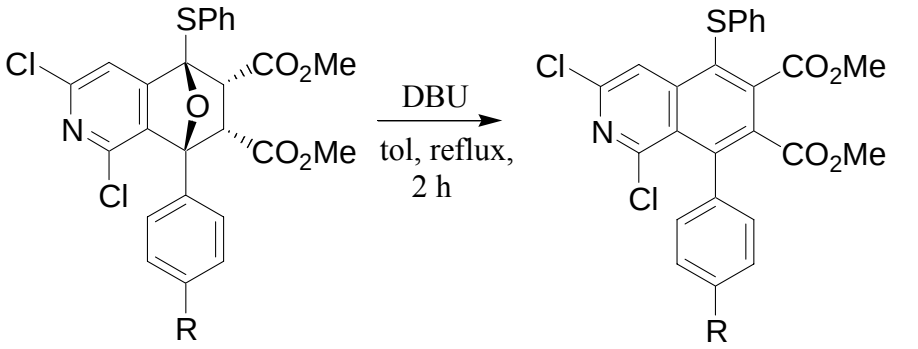


Figure 14

Chemically, we have been able to accomplish aromatization of **132-134** with DBU in refluxing toluene to give **163-165** in 45-55% yields (Scheme 29). Structures of these products were established from spectral data. For example, ^{1}H NMR spectrum of **163** shows appearance of signals at δ 3.43 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 7.15-7.32 (m, 6H, aromatic protons), 7.35-7.48 (m, 4H, aromatic protons), 8.37 (s, 1H, pyridine proton) and disappearance of signals at 3.61 (d, 1H, J = 11.2 Hz, C*H*), 4.16 (d, 1H, J = 11.2 Hz, C*H*) corresponding to starting material thus indicating that is a fully aromatized compound. In ^{13}C NMR, the disappearance of methine carbon signals of **132**

at δ 52.6 and 53.6 accounts for the structure of **163**. Structure of **163** is further confirmed from X-ray single crystal structure determination.[49] Figures 15 and 16 represent the ORTEP and crystal packing perspective view of **163**. Incidentally, initial attempts for the ring opening of **132-134** using a variety of other reagents, e.g. MeOH/HCl, *p*-TsOH in refluxing toluene and CF_3COOH were ineffective; in each case the starting material was recovered intact. The synthesis of these compounds, e.g., **165** can also be conducted in one pot by exposing sulfoxide **127** to the modified Pummerer conditions and then adding DBU to the reaction mixture.

Scheme 29



132-134

163; R = H 53%
164; R = Me 55%
165; R = OMe 45%

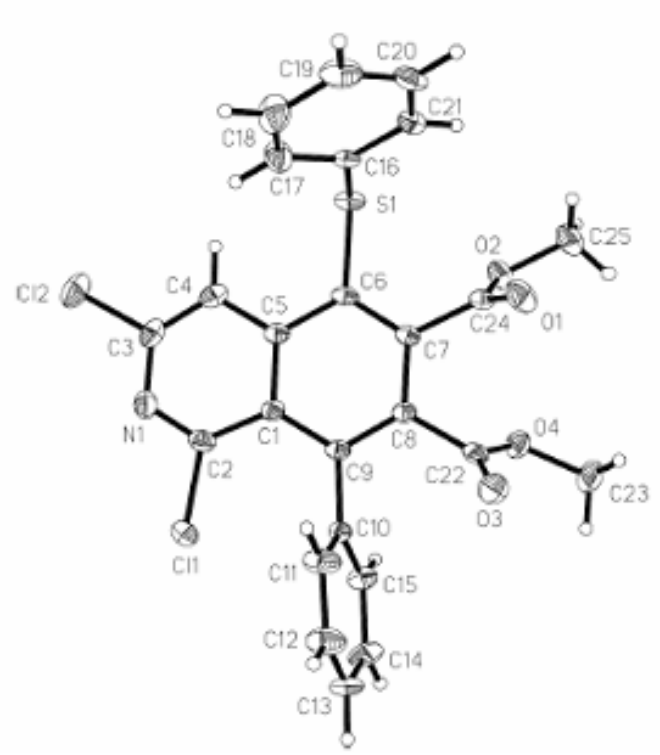


Figure 15. ORTEP prospective view of **163**

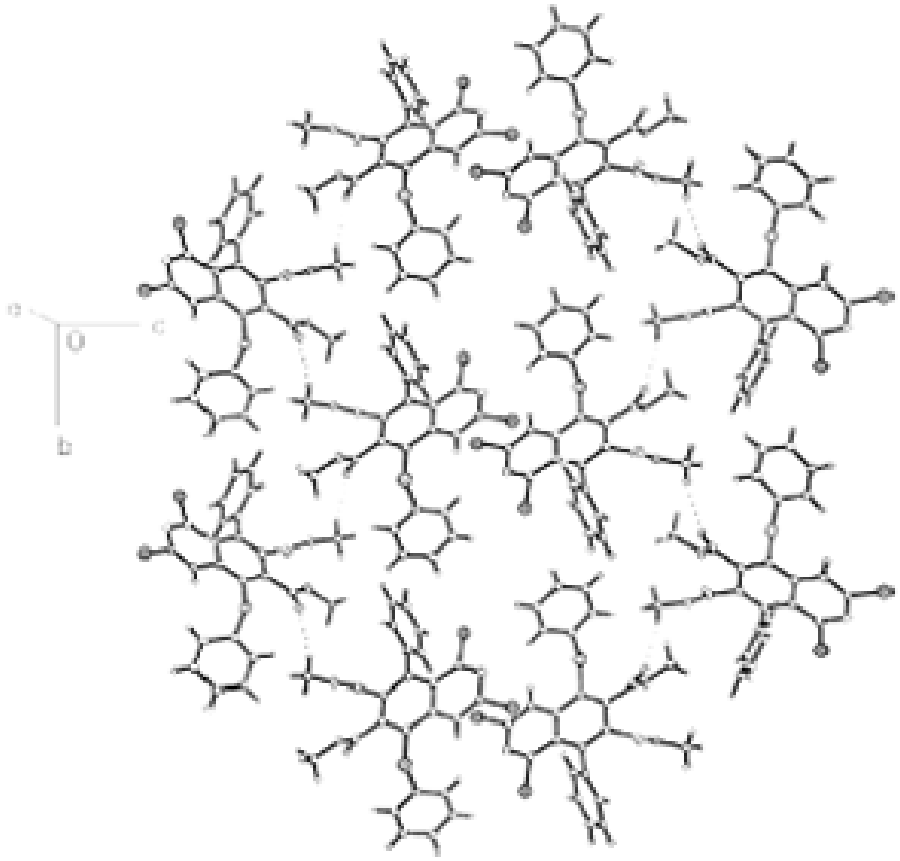


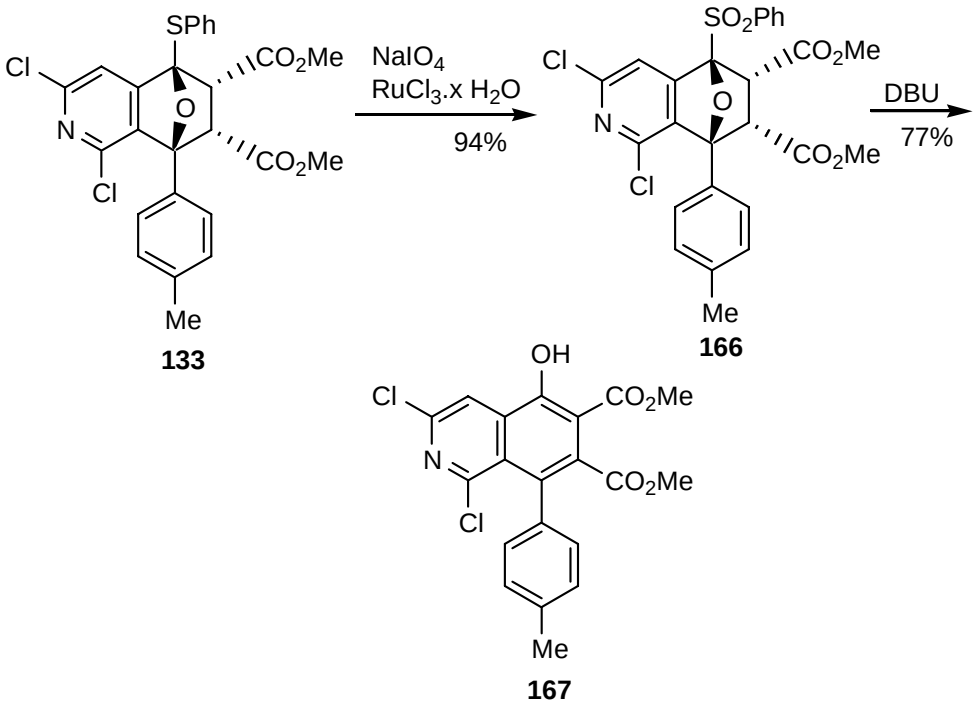
Figure 16. Crystal packing diagram of **163**

Furthermore, the usefulness of the sequential Pummerer-Diels-Alder reaction was demonstrated through the synthesis of a heterolignan with a built-in lactone ring via oxidation of the initial [4+2]-cycloadduct followed by extrusion of phenyl sulfinate and elaboration of the resulting hydoxylated isoquinoline derivative (Scheme 30 and 31). Thus, the phenylsulfanyl group present in **133** was oxidized[37a] using $NaIO_4$ in presence of a catalytic amount of $RuCl_3$ to give sulfone **166** in very good yield within 2h. The presence of the molecular ion peak at *m/*z 579 ($[M + NH_4]^+$, $C_{26}H_{24}Cl_2N_2O_6S$) in DCI-MS and presence of sulfonyl absorption band at 1164 cm^{-1} in IR spectrum suggested the formation of sulfone **166**. The ^1H and ^{13}C NMR of **166** also agreed with the structure. Ring opening followed by extrusion of phenylsulfinate was done by exposure of **166** to DBU in refluxing toluene to give the hydroxy isoquinoline derivative **167** (Scheme 30). The characteristic signals for **167** in ^1H NMR (200 MHz, $CDCl_3$) are δ 8.31 (s, 1H, pyridine proton), 12.42 (s, 1H, phenolic OH) and disappearance of signals from **166** at δ 4.21 (d, 1H, J = 11.2 Hz), 4.29 (d, 1H, J = 11.2 Hz). The presence of the molecular ion peak at *m/*z 437 ($[M + NH_4]^+$, $C_{20}H_{19}Cl_2N_2O_5$) in DCI-MS and *m/z* 420.0410 ($[M+H]^+$, $C_{20}H_{16}Cl_2NO_5$) in HRMS confirms the elimination of SO_2Ph group and formation of the isoquinol derivative **167**.

With the isoquinol derivative **167** in hand we turned our attention to the synthesis of lignanolides by converting the diesters to corresponding lactone e.g. **117**. We found from the literature that the analogous naphthol derivatives e.g. **93** can be easily reduced to lactones by sodium borohydride in methanol,[50, 37a] although reduction of esters by sodium borohydride is unusual. In this case the initial complexion of the reagent with the adjacent phenol group helps selective reduction of the desired ester group. Accordingly,

sodium borohydride should selectively reduce the diester **167** to the desired lignanolide **169**.[50, 37a] Unfortunately, we failed to obtain any lactone from the sodium borohydride reduction. Rather we got a mixture of products which were not characterized further. We

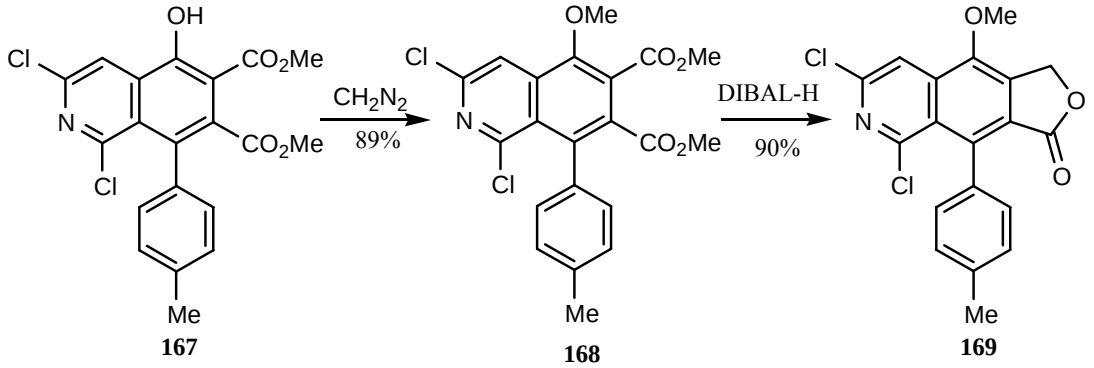
Scheme 30



overcame this problem by prior methylation of the hydroxy group and DIBAL-H reduction of the resulting methyl ether **168** to give the heterolignan **169** directly (Scheme 31). The presence of molecular ion peak at *m/z* 374 ($[M+H]^+$, $C_{19}H_{14}Cl_2NO_3$) in the mass spectrum and carbonyl absorption band at 1779 cm^{-1} due to the γ-lactone in IR spectrum revealed the formation of **169**. In ^1H NMR, the disappearance of methyl ester signals at δ 3.34, 3.93 (corresponding to starting material **168**) and the appearance of characteristic singlets at 2.45 and 4.19 accounted for the tolyl C*H*$_3$ and O*Me* group

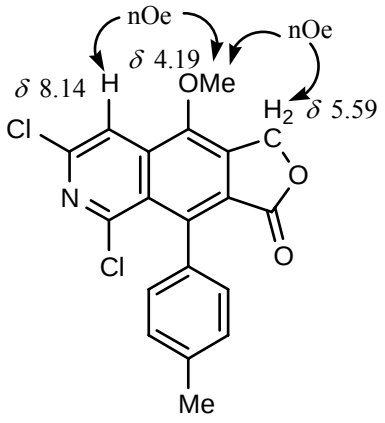
of **169**, respectively; also, the singlets at δ 5.59 for -CH_2OCO group and δ 8.14 for one proton attached to the pyridine ring explained the structure. Additionally, in ^{13}C NMR

Scheme 31



the disappearance of the two methyl carbon signals at δ 52.2, 53.0 (due to two CO_2CH_3 of **168**) and one quaternary carbon signal at 165.4 (due to one of the *C*OO of **168**) and appearance of methylene carbon signal (*C*H_2OCO) at 65.8 confirms the reduction of diester to lactone **169**. Other respective signals in ^{13}C NMR at 21.5 (q), 59.9 (q), 114.8 (d), 124.5 (s), 125.7 (s), 128.5 (d), 129.0 (s), 129.3 (d), 131.7 (s), 137.0 (s), 137.7 (s), 138.2 (s), 145.3 (s), 147.8 (s), 152.5 (s), 167.3 (s) fully support the number of carbons and their nature.

The position of the lactone carbonyl in **169** was determined by NOE experiments, which show a significant enhancement of the OMe signal at δ 4.19 upon irradiation of the adjacent CH_2 singlet at δ 5.59. Furthermore, on irradiation of O*Me* signal at δ 4.19 shows an enhancement at δ 5.59 (CH_2OCO signal), as well as at δ 8.14 due to adjacent pyridine proton. The selectivity in the ester reduction stems from the fact that the tolyl group which is orthogonal to the plane of the isoquinoline ring effectively shields the adjacent carbomethoxy group.



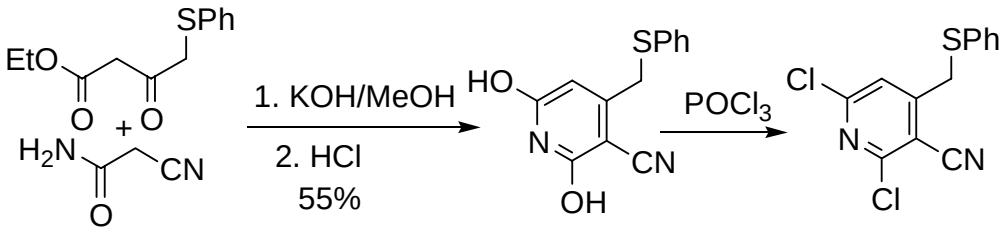
169

5. Conclusion

In conclusion, we have demonstrated that the sequential Pummerer-Diels-Alder reaction sequence is suited to efficient synthesis of a variety of heterocyclic ring systems including some 1-arylnaphthalene lignans. The key intermediates in this cascade process are α-thiosubstituted furo[3,4-*c*]pyridines, which in some cases can be isolated and independently reacted with a suitable dienophile to give [4+2]-cycloadducts. However, we found it to be most convenient to carry out these reactions in an all tandem fashion. In addition intramolecular trapping of the *in-situ* generated furo[3,4-*c*]pyridine is an efficient route for the rapid access to annulated isoquinoline derivatives. Our results clearly indicate that this methodology provides rapid entry into heteroaromatic *o*-quinodimethanes.

6. Experimental

2,6-Dichloro-4-[(phenylthio)methyl]nicotinonitrile (**110**).



110

(a) A mixture containing cyanoacetamide (5.06 g, 60.21 mmol) and ethyl 4-(phenylthio)acetoacetate[51] (14.33 g, 60.21 mmol) in 50 mL of methanol was warmed to attain solution and potassium hydroxide (4.14 g, 73.82 mmol) dissolved in 20 mL of methanol was added dropwise with stirring. The mixture was heated reflux; after 2 h a brown precipitate formed and heating was continued for an additional 5 h. Then the reaction mixture was cooled and 2,6-dihydroxy-4-[(phenylthio)methyl]nicotinonitrile monopotassium salt so formed was separated by filtration, dissolved in warm water, cooled, and acidified with concentrated hydrochloric acid. The product was separated by filtration, washed with cold methanol, dried in air, and finally further dried at 120-130 °C in vacuo for 5h to give 8.4 g (55%) of 2,6-dihydroxy-4-[(phenylthio) methyl]nicotinonitrile as off-white solid: chars at 268 °C, mp 275-278 °C.

IR (KBr) 3100, 2221 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:DMSO-d_6) δ 3.98 (s, 2H), 5.68 (s, 2H), 7.10-7.43 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$, DMSO-d_6) δ 36.1 (t), 89.2 (s), 92.1 (d), 116.0 (s), 126.7 (d), 128.8 (d), 129.7 (d), 134.1 (s), 159.0 (s), 161.3 (s), 161.8 (s).

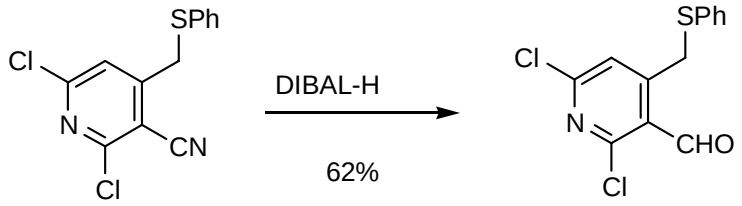
(b) A mixture containing 2,6-dihydroxy-4-[(phenylthio) methyl]nicotinonitrile (4 g, 15.5 mmol) and $POCl_3$ (5.8 mL, 62.0 mmol) was heated in a sealed tube at 150 °C for 9 h. It was then cooled to room temperature and transferred into 100 mL of ice cold water. The mixture was filtered with repeated washings with water. The residue was dissolved in hot methanol, heated for 10 min with activated charcoal, filtered, and concentrated. The resulting brown oil was purified by chromatography (EtOAc:petroleum ether 1:99) to give 2.45 g (54%) of **110** as a yellow solid. A purer sample was obtained by recrystallization from petroleum ether to give colorless needles: mp 117 °C (mp 118-119 °C, reported by Dr. S. Basak from this laboratory).

IR (KBr) 2231, 1567, 1530, 1336 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 4.12 (s, 2H), 7.13 (s, 1H), 7.32 (br s, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) 37.5 (t), 109.2 (s), 112.6 (s), 123.1 (d), 128.6 (d), 129.3 (d), 131.9 (s), 132.5 (d), 152.5 (s), 153.6 (s), 156.3 (s).

2,6-Dichloro-4-[(phenylthio)methyl]nicotinaldehyde (**111**)



110 **111**

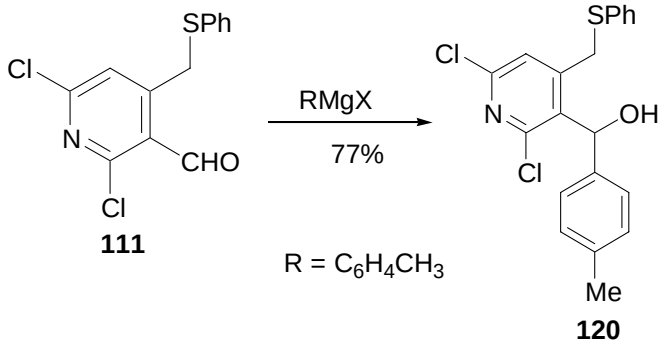
To a stirred solution of **110** (4 g, 13.56 mmol) in 60 mL of CH_2Cl_2 cooled to -78 ^oC was added 15 mL of DIBAL-H (1.0 M solution in toluene) dropwise over a period of 1h. The resulting mixture was allowed to attain room temperature. After 2 h of stirring at room temperature the solution was quenched with saturated aqueous NH_4Cl at 0 ^oC, stirred for another 1 h at that temperature and then acidified with 3 N HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography (EtOAc: petroleum ether 1:99) to give 2.7 g (67%) of the *title compound* **111** as white crystalline solid: mp. 59-60 °C (mp. 61-62 °C, reported by Dr. S. Basak from this laboratory).

IR (KBr) 1688, 1565, 1526, 1317 cm^{-1}.

^1H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 4.36 (s, 2H), 7.00 (s, 1H), 7.28 (br s, 5H), 10.42 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 36.2 (t), 124.9 (s), 125.0 (d), 128.0 (d), 129.1 (d), 132.2 (d), 133.3 (s), 153.4 (s), 154.2 (s), 154.4 (s), 190.2 (d).

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methylphenyl)methanol** (**120**).



To a stirred solution of aldehyde **111** (1 g, 3.5 mmol) in 20 mL of dry THF was added dropwise a tolylmagnesium bromide solution (16.8 mL, 0.4 M) [prepared from *p*-bromotoluene (1.23 mL, 10 mmol) and Mg (480 mg, 20 mmol) in 24 mL of THF] over a period of 10 min at -78 °C. During addition a blood red color was formed. After 1h of stirring the mixture was slowly warmed to 0 °C and then quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by chromatography (EtOAc:petroleum ether 10:90) giving 950 mg (73%) of **120** as a white crystalline solid: mp 129 -131 °C.

IR (KBr) 3371, 1575, 1524, 1104 cm^{-1}.

^1H NMR (200 MHz, CDCl3:CCl4 7:3) δ 2.36 (s, 3H), 3.46 (s, 1H), 3.84 (d, 1H, J_{AB} = 15.3 Hz), 4.26 (d, 1H, J_{AB} = 15.3 Hz), 6.57 (br s, 1H), 6.82-7.41 (m, 10H).

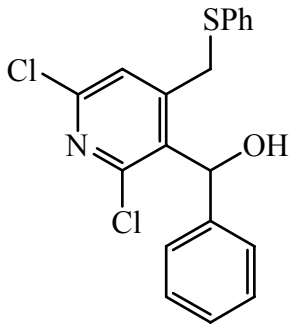
^{13}C NMR (50 MHz, $CDCl_3$: CCl_4 7:3) δ 21.1 (q), 35.4 (t), 70.9 (d), 125.0 (d), 125.2 (d), 127.0 (d), 129.0 (d), 129.3 (d), 130.1 (d), 134.3 (s), 134.4 (s), 137.2 (s), 137.6 (s), 149.5 (s), 149.8 (s), 152.9 (s).

FAB MS *m/z* (rel intensity) 390 ($[M + H]^+$, 100), 372 ($[M - H_2O]H^+$, 26), 279 (31), 264 (42), 227 (10), 219 (5), 188 (4), 120 (10).

HRMS (FAB) calcd for $C_{20}H_{18}Cl_2NOS$ $(M+H)_+$ *m/z* 390.0486, found 390.0486.

Anal. Calcd for $C_{20}H_{17}Cl_2NOS$: C, 61.56; H, 4.38; N, 3.58. Found: C, 61.34; H, 4.19; N, 3.85.

{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}(phenyl)methanol (**119**)



119

was prepared by a similar method starting from aldehyde **111** (820 mg, 2.75 mmol) and bromobenzene in 77% yield as a white crystalline solid: mp 146-148 °C.

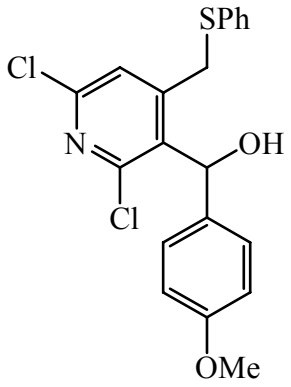
IR (KBr) 3506, 1605, 1571, 1326, 1066 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.2 (br s, 1H), 3.80 (d, 1H, J_{AB} = 15.2 Hz), 4.23 (d, 1H, J_{AB} = 15.2 Hz), 6.62 (s, 1H), 6.98-7.45 (m, 11H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 35.5 (t), 70.9 (d), 125.0 (d), 125.1 (d), 127.1 (d), 127.5 (d), 128.5 (d), 129.0 (d), 130.3 (d), 133.9 (s), 134.0 (s), 140.4 (s), 149.5 (s), 149.9 (s), 152.6 (s).

Anal. Calcd for $C_{19}H_{15}Cl_2NOS$: C, 60.66, H, 4.01; N, 3.72. Found: C, 60.61; H, 3.91; N, 3.85.

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methoxyphenyl)methanol** (**121**)



121

was prepared by a similar method starting from aldehyde **111** (450 mg, 1.51 mmol) and *p*-bromoanisol in 69% yield as a white crystalline solid: mp 116-118 °C.

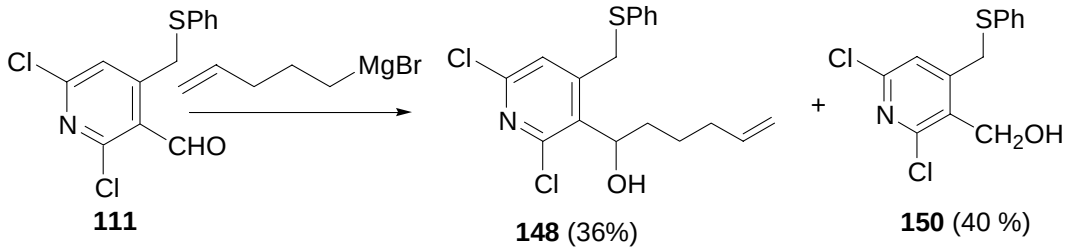
IR (KBr) 3351, 1569, 1525, 1098 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.50 (br s, 1H), 3.78 (s, 3H), 3.86 (d, 1H, J_{AB} = 15.3 Hz), 4.27 (d, 1H, J_{AB} = 15.2 Hz), 6.56 (br s, 1H), 6.72-7.35 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 35.5 (t), 55.3 (q), 70.8 (d), 114.1 (d), 125.1 (d), 126.6 (d), 127.2 (d), 129.1 (d), 130.3 (d), 132.6 (s), 134.3 (s), 149.5 (s), 149.8 (s), 152.9 (s), 159.1 (s).

Anal. Calcd. for $C_{20}H_{17}Cl_2NO_2S$: C, 59.13; H, 4.21; N, 3.44. Found: C, 59.41; H, 4.31; N, 3.19.

1-{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}- hex-5-en-1-ol (148)



was prepared by a similar method starting from aldehyde **111** (400 mg, 1.34 mmol) and 5-bromo-1-pentene in 36% yield.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.31- 2.18 (m, 6H), 4.18 (d, 1H, J_{AB} = 13.3 Hz), 4.43 (d, 1H, J_{AB} = 13.3 Hz), 4.89-5.08 (m, 2H), 5.27-5.37 (m, 1H), 5.62-5.91 (m, 1H), 7.01 (s, 1H), 7.19-7.40 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 70:30) δ 25.4 (t), 33.3 (t), 35.8 (t), 36.4 (t), 71.1 (d), 115.1 (t), 125.4 (d), 127.7 (d), 129.2 (d), 131.7 (d), 134.4 (s), 134.5 (s), 138.0 (d), 148.3 (s), 148.9 (s), 151.7 (s).

Anal. Calcd for $C_{18}H_{19}Cl_2NOS$: C, 58.71; H, 5.19; N, 3.80. Found: C, 58.93; H, 5.31; N, 3.49.

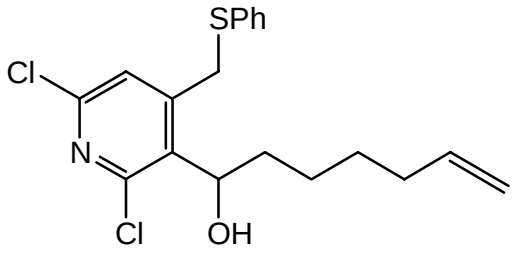
2, 6-Dichloro-4-((phenylthio)methyl)pyridine-3-yl)methanol (**150**) was formed in the above reaction as an oil in 40% yield.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 4. 12 (s, 2H), 4.80 (s, 2H), 6.89 (s, 1H), 7.28 (bs, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 36.6, 58.2, 124.3, 128.2, 129.3, 131.1, 132.0, 133.0, 149.3, 151.1, 151.9.

HRMS (CI) calcd for $C_{13}H_{12}Cl_2NOS$ $(M)^+$ *m/z* 300.0017, found 300.0009.

1-{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}- hept-6-en-1-ol (**149**)



149

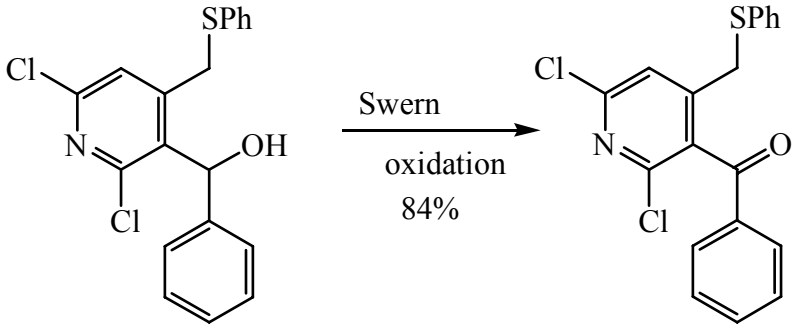
was prepared by a similar method starting from aldehyde **111** (440 mg, 1.47 mmol) and 6-bromo-1-hexene in 32% yield as a yellow oil.

IR ($CHCl_3$) 3308, 1568, 1533, 1307 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 70:30) δ 1.28-2.15 (m, 8H), 2.47 (br s, 1H), 4.27 (d, 1H, J_{AB} = 13.4 Hz), 4.44 (d, 1H, J_{AB} = 13.4 Hz), 4.90-5.05 (m, 2H), 5.21-5.45 (m, 1H), 5.65- 5.85 (m, 1H), 7.04 (s, 1H), 7.27-7.40 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 25.5 (t), 28.4 (t), 33.5 (t), 36.1 (t), 36.4 (t), 71.1 (d), 114.5 (t), 125.3 (d), 127.7 (d), 128.9 (d), 131.6 (d), 134.4 (s), 134.6 (s), 138.5 (d), 148.2 (s), 148.9 (s), 151.7 (s).

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}- **(phenyl)methanone** (**122**).



119 **122**

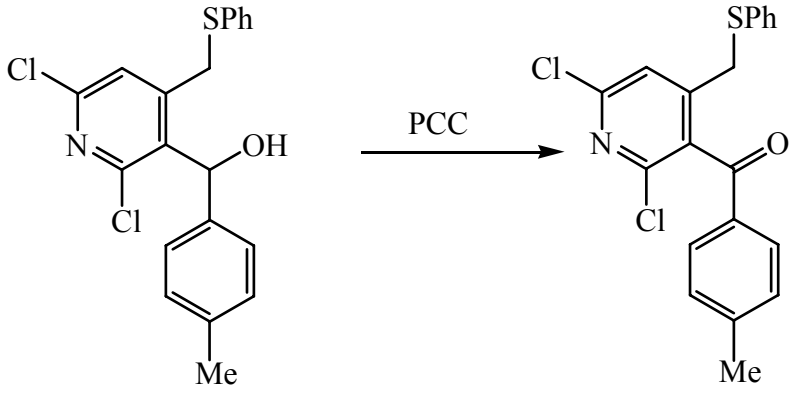
To a stirred solution of oxalyl chloride (0.278 mL, 3.13 mmol) in 10 mL of CH_2Cl_2 cooled at -60 °C was added DMSO (0.453 mL, 6.39 mmol) in 5 mL of CH_2Cl_2 dropwise via dropping funnel in 15 min under argon atmosphere. The mixture was stirred for 30 min followed by addition of **119** (800 mg, 2.13 mmol) in 10 mL of CH_2Cl_2 over a period of 10 min. After 30 min of stirring Et_3N (1.5 mL, 10.65 mmol) was added and the reaction mixture was allowed to attain room temperature and stirred for 1 h. Then 100 mL of cold H_2O was added to the mixture. The organic layer was separated and washed with 1% HCl and brine. Finally the organic fraction was concentrated in vacuo and purified by chromatography (EtOAc:petroleum ether 5:95) to give 670 mg of **122** in 84% yield.

IR (KBr) 1666, 1602, 1555, 1332 cm^{-1}.

^{1}H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 3.90 (s, 2H), 7.00-7.85 (m, 11H).

^{13}C NMR (50 MHz $CDCl_3$:CCl_4 7:3) δ 35.7 (t), 123.7 (d), 127.6 (d), 128.9 (d), 129.2 (d), 129.6 (d), 130.9 (d), 132.7 (s), 133.5 (s), 134.5 (d), 135.8 (s), 146.7 (s), 150.8 (s), 151.1 (s), 192.5 (s).

{**2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl**}**(4-methylphenyl)methanone** (**123**)



120 **123**

To a stirred solution of **120** (2 g, 5.12 mmol) in 20 mL of dry CH_2Cl_2 was added PCC (1.7 g, 7.7 mmol) at room temperature. After 1.5 h of stirring the solution was filtered over a short Celite pad. The yellow solution was then concentrated under reduced pressure and purified by chromatography (EtOAc:petroleum ether 5:95) to give 1.55 g (78%) of **123** as a white solid: mp 105-107 °C.

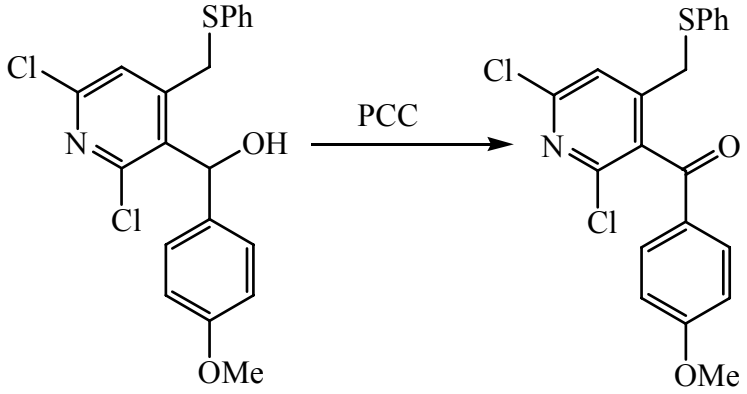
IR (KBr) 1658, 1602, 1565, 1325 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$: CCl_4 7:3) δ 2.42 (s, 3H), 3.90 (s, 2H), 7.05-7.35 (m, 8H), 7.64 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.9 (q), 35.6 (t), 123.6 (d), 127.5 (d), 129.1 (d), 129.7 (d), 129.8 (d), 130.8 (d), 133.0 (s), 133.4 (s), 133.6 (s), 145.7 (s), 146.7 (s), 150.6 (s), 150.9 (s), 192.0 (s).

Anal. Calcd for $C_{20}H_{15}Cl_2NOS$: C, 61.87; H, 3.89; N, 3.60. Found: C, 62.09; H, 3.97; N, 3.83.

{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}(4-methoxyphenyl)methano-ne (124)



121 **124**

was obtained by the PCC oxidation of alcohol **121** (400 mg, 0.98 mmol) in 96% yield as a yellow oil.

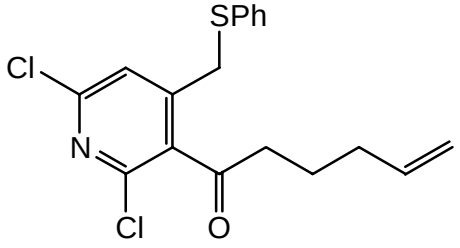
IR (KBr) 1660, 1595, 1564, 1343 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.88 (s, 3H), 3.90 (s, 2H), 6.90 (d, 2H, *J* = 9.1 Hz), 7.12-7.28 (m, 6H), 7.70 (d, 2H, *J* = 8.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 70:30) δ 35.6 (t), 55.4 (q), 114.2 (d), 123.4 (d), 127.5 (d), 128.9 (s), 129.1 (d), 130.8 (d), 132.0 (d), 133.0 (s), 133.7 (s), 146.7 (s), 150.5 (s), 150.7 (s), 164.6 (s), 190.7 (s).

Anal. Calcd for $C_{20}H_{15}Cl_2NO_2S$: C, 59.41; H, 3.74; N, 3.46. Found: C, 59.22; H, 3.63; N, 3.59.

1-{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}-hex-5-en-1-one (**151**)



151

was obtained by the PCC oxidation of **148** (170 mg, 0.462 mmol) in 83% yield as a yellow oil.

IR ($CHCl_3$) 1707, 1565, 1530, 1325 cm^{-1}.

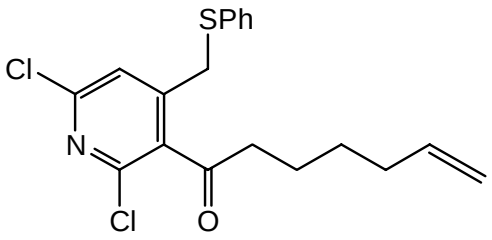
^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.68-1.97 (m, 2H), 2.08-2.19 (m, 2H), 2.87 (t, 2H, *J* = 7.3 Hz), 3.88 (s, 2H), 4.97-5.12 (m, 2H), 5.67-5.91 (m, 1H), 6.99 (s, 1H), 7.13-7.42 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.3 (t), 32.8 (t), 36.1 (t), 43.4 (t), 115.6 (t), 123.9 (d), 128.2 (d), 129.4 (d), 131.9 (d), 133.3 (s), 134.8 (s), 137.5 (d), 145.7 (s), 149.7 (s), 150.3 (s), 202.7 (s).

DCI-MS *m/z* (rel intensity) 383 ($[M + NH_4]^+$, 82), 366 ($[M + H]^+$, 100).

HRMS (FAB) calcd for $C_{18}H_{18}Cl_2NOS$ $(M + H)^+$ *m/z* 366.0486, found 366.0500.

1-{2,6-Dichloro-4-[(phenylthio)methyl]pyridin-3-yl}-hept-6-en-1-one (**152**)



152

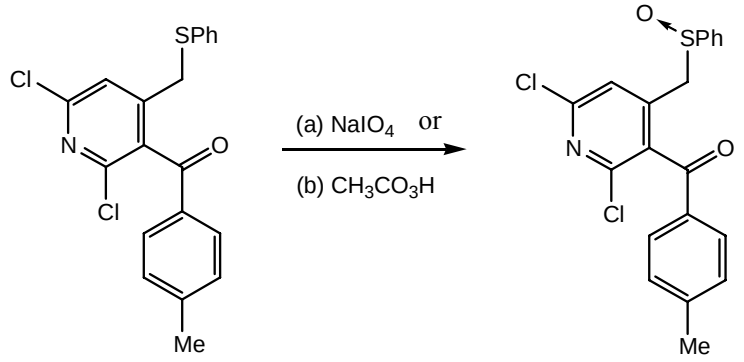
was obtained by PCC oxidation of **149** (110 mg, 0.29 mmol) in 82% yield as a yellow oil.

IR ($CHCl_3$) 1702, 1567, 1532, 1329 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.38-1.61 (m, 2H), 1.65-1.85 (m, 2H), 1.92-2.21 (m, 2H), 2.86 (t, 2H, *J* = 7.2 Hz), 3.87 (s, 2H), 4.92-5.13 (m, 2H), 5.72-5.91 (m, 1H), 6.99 (s, 1H), 7.16-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.7 (t), 28.2 (t), 33.5 (t), 36.1 (t), 43.9 (t), 115.0 (t), 124.0 (d), 128.2 (d), 129.4 (d), 131.9 (d), 133.3 (s), 134.9 (s), 138.1 (d), 145.6 (s), 149.7 (s), 150.3 (s), 202.8 (s).

{**2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl**}**-(4-methylphenyl)metha-none** (**126**).



123 **126**

(a) To a slurry of **123** (430 mg, 1.10 mmol) in a 1:1 mixture of CH_3OH and H_2O (6 mL) was added $NaIO_4$ (246 mg, 1.15 mmol) at 0 °C; then the mixture was warmed to room temperature. After 15-20 days 5 mL of CH_2Cl_2 was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified over chromatography (EtOAc:petroleum ether 20:80) to give 380 mg (85%) of sulfoxide **126** as a white solid: mp 162-164 °C.

IR (KBr) 1668, 1603, 1570, 1532, 1327, 1085, 1045 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.45 (s, 3H), 3.79 (d, 1H, *J* = 12.8 Hz), 3.92 (d, 1H, *J* = 12.8 Hz), 7.15-7.85 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.8 (q), 60.4 (t), 123.7 (d), 125.2 (d), 129.3 (d), 129.7 (d), 129.9 (d), 131.7 (d), 133.4 (s), 133.5 (s), 142.5 (s), 143.5 (s), 145.9 (s), 147.0 (s), 150.7 (s), 191.9 (s).

DCI-MS *m/z* (rel intensity) 421 ($[M + NH_4]^+$, 84), 404 ($[M + H]^+$, 100).

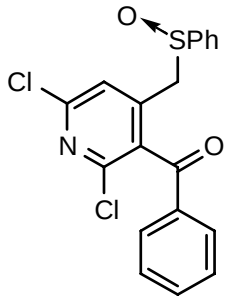
HRMS (FAB) calcd. for $C_{20}H_{16}Cl_2NO_2S$ $(M + H)^+$ *m/z* 404.0279, found 404.0262.

Anal. Calcd for $C_{20}H_{15}Cl_2NO_2S$: C, 59.43; H, 3.73; N, 3.46. Found: C, 9.29; H, 3.78; N, 3.52.

(b) To a stirred solution of **123** (1 g, 2.57 mmol) in ether (20 mL) was added peracetic acid (32 wt %, 10 mL) at 0°C and stirring was continued for additional 10 min. Then the reaction mixture was refluxed for 20 min during which white precipitates are formed. The reaction mixture was triturated with excess of water (50 mL) and ether (50 mL) and the organic layer was separated. The aqueous layer was extracted with ether three times and the combined organic layer was wash with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified over chromatography (EtOAc:petroleum ether 20:80) to give 720 mg (69.2 %) of sulfoxide **126** as a white solid: mp 162-164 °C. and remaining 100 mg of starting material.

The ^1H NMR of the product is identical with that obtained in (a).

{**2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl**}**-(phenyl)methanone** (**125**)



125

was obtained by $NaIO_4$ mediated oxidation of sulfide **122** (640 mg, 1.71 mmol) in 68% yield as a yellow oil.

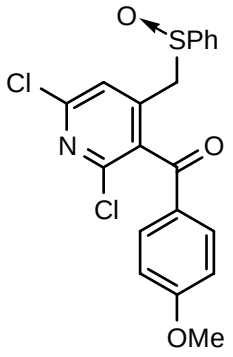
IR (KBr) 1665, 1605, 1577, 1532, 1333, 1085, 1045 cm^{-1}.

^1H NMR (200 MHz $CDCl_3$:CCl_4 7:3) δ 3.74 (d, 1H, *J* = 12.9 Hz), 3.90 (d, 1H, *J* = 12.9 Hz), 7.18 (s, 1H), 7.22-7.92 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 60.1 (t), 123.7 (d), 125.3 (d), 129.0 (d), 129.3 (d), 129.7 (d), 131.8 (d), 133.3 (s), 134.8 (d), 135.8 (s), 142.5 (s), 143.7 (s), 147.0 (s), 150.9 (s), 192.4 (s).

Anal. Calcd for $C_{19}H_{13}Cl_2NO_2S$: C, 58.48; H, 3.35; N, 3.58. Found: C, 58.19; H, 3.13; N, 3.68.

{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}-(4-methoxyphenyl)methanone (127)



127

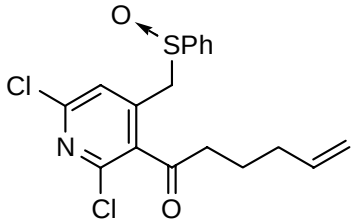
was obtained by $NaIO_4$ mediated oxidation of keto sulfide **124** (390 mg, 0.96 mmol) in 91% yield as a white crystalline solid: mp 142-143 °C.

IR (KBr) 1687, 1595, 1324, 1153, 1041 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.73 (d, 1H, *J* = 12.9 Hz), 3.84 (s, 3H), 3.87 (d, 1H, *J* = 12.9 Hz), 6.90 (d, 2H, *J* = 8.9 Hz), 7.14 (s, 1H), 7.24-7.58 (m, 5H), 7.72 (d, 2H, *J* = 8.69).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 55.5 (q), 60.4 (t), 114.3 (d), 123.7 (d), 125.1 (d), 128.9 (s), 129.3 (d), 131.6 (d), 132.2 (d), 133.7 (s), 142.7 (s), 143.5 (s), 146.9 (s), 150.5 (s), 164.8 (s), 190.5 (s).

1-{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}hex-5-en-1-one (153)



153

was obtained by $NaIO_4$ mediated oxidation of keto sulfide **151** (90 mg, 0.246 mmol) by $NaIO_4$ in 85% yield as a yellow oil.

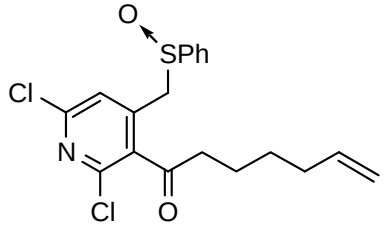
IR ($CDCl_3$) 1702, 1530, 1328, 1123, 1085 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 1.78-1.95 (m, 2H), 2.12-2.27 (m, 2H), 2.96-3.02 (m, 2H), 3.71 (d, 1H, *J* = 12.8 Hz), 4.12 (d, 1H, *J* = 12.9 Hz), 4.99-5.11 (m, 2H), 5.71-5.88 (m, 1H), 6.83 (s, 1H), 7.42-7.58 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.6 (t), 32.7 (t), 43.6 (t), 59.0 (t), 115.5 (t), 123.9 (d), 125.3 (d), 129.5 (d), 132.0 (d), 136.0 (s), 137.6 (d), 141.7 (s), 142.0 (s), 146.0 (s), 150.3 (s), 203.4 (s).

Anal. Calcd for $C_{18}H_{17}Cl_2NO_2S$: C, 56.56; H, 4.47; N, 3.66. Found: C, 56.69; H, 4.53; N, 3.51.

1-{2,6-Dichloro-4-[(phenylsulfinyl)methyl]pyridin-3-yl}hept-6-en-1-one (154)



154

was obtained by $NaIO_4$ mediated oxidation of keto sulfide **152** (100 mg, 0.263 mmol) by $NaIO_4$ in 77% yield as yellow oil.

IR ($CHCl_3$) 1702, 1633, 1563, 1392, 1094, 1048 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.38-2.19 (m, 6H), 2.81-3.09 (m, 2H), 3.72 (d, 1H, *J* = 12.9 Hz), 4.11 (d, 1H, *J* = 12.9 Hz), 4.89-5.16 (m, 2H), 5.69-5.91 (m, 1H), 6.85 (s, 1H), 7.41-7.82 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 22.9 (t), 28.2 (t), 33.6 (t), 43.7 (t), 57.7 (t), 114.9 (t), 126.2 (d), 128.4 (d), 129.7 (d), 134.7 (d), 136.5 (s), 138.2 (s), 138.3 (d), 139.2 (s), 146.5 (s), 150.6 (s), 203.3 (s).

Anal. Calcd for $C_{19}H_{19}Cl_2NO_2S$; C, 57.57; H, 4.82; N, 3.53. Found: C, 57.80; H, 5.01; N, 3.51.

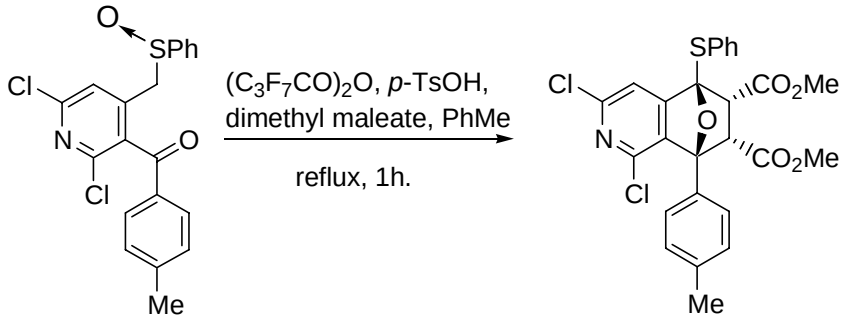
General procedure for Pummerer-Diels-Alder reaction

Padwa's conditions (Ac_2O/ *p*-TsOH): A mixture containing acetic anhydride (10 mmol), appropriate dienophile (4 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dry toluene (10 mL) was heated at reflux under argon. To this mixture was added a toluene solution of keto-sulfoxide (1 mmol) dropwise over a period of 10 min. After addition was complete the yellow mixture was heated at reflux for an additional 1 h. The

reddish yellow solution was cooled and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography.

Modified conditions ($(C_3F_7CO)_2O$/ *p*-TsOH): A mixture containing heptafluorobutyric anhydride (10 mmol), appropriate dienophile (4 mmol), and a catalytic amount of *p*-toluenesulfonic acid was heated at reflux under argon. To this mixture was added keto-sulfoxide (1 mmol) in dry toluene dropwise over a period of 10 min. After complete addition, the yellow mixture was heated at reflux for an additional 1 h. The reddish yellow solution was cooled and washed with saturated $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography.

Dimethyl 3,5-dichloro-1-(4-methylphenyl)-8-(phenylthio)-11-oxa-4-azatricyclo-[6.2.1.0^{2,7}] - undeca-2,4,6-triene-9,-10-dicarboxylate (133)



126 **133**

was prepared by the treatment of ketosulfoxide **126** (100 mg, 0.247 mmol) with dimethyl maleate (0.124 mL, 1 mmol) under modified conditions in 37% yield as a yellowish white solid: mp 199-200 °C.

IR (KBr) 1742, 1633, 1595, 1336 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.41 (s, 3H), 3.56 (s, 6H), 3.58 (d, 1H, *J* = 11 Hz), 4.14 (d, 1H, *J* = 11 Hz), 7.19-7.69 (m, 10H).

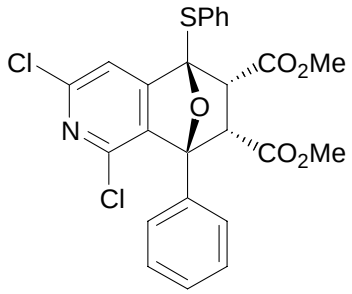
^{13}C NMR (50 MHz, CDCl3:CCl_4 7:3) δ 21.4 (q), 52.0 (q), 52.4 (q), 52.6 (d), 53.6 (d), 90.0 (s), 93.7 (s), 118.0 (d), 128.1 (d), 129.2 (d), 129.6 (d), 131.1 (s), 135.5 (d), 137.8 (s), 139.4 (s), 143.8 (s), 148.8 (s), 157.5 (s), 167.7 (s), 169.0 (s).

FAB MS *m*/*z* (rel intensity) 530 ($[M + H]^+$, 11), 386 (3), 273 (3), 235 (6), 165 (4).

HRMS (FAB) calcd for $C_{26}H_{22}Cl_2NO_5S$ $(M+H)^+$ *m/z* 530.0596, found 530.0589.

Anal. Calcd for $C_{26}H_{21}Cl_2NO_5S$: C, 58.88; H, 3.98; N, 2.64. Found: C, 58.65; H, 3.94; N, 2.87.

Dimethyl 3,5-dichloro-1-phenyl-8-(phenylthio)-11-oxa-4-azatricyclo[6.2.1.$0^{2,7}$]-undeca-2,4, 6-triene-9,10-dicarboxylate (132)



132

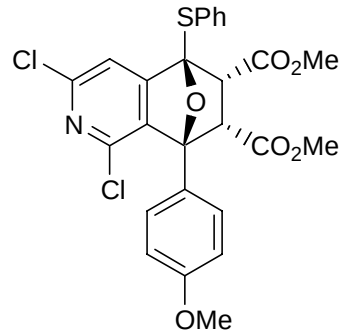
was prepared in a similar manner (modified conditions) from keto sulfoxide **125** (100 mg, 0.26 mmol) in 33% yield as a yellowish white solid: mp 174-175 °C.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.57 (s, 6H), 3.61 (d, 1H, *J* = 11.2 Hz), 4.16 (d, 1H, *J* = 11.2 Hz), 7.25-7.70 (m, 11H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 51.9 (q), 52.3 (q), 52.5 (d), 53.5 (d), 89.8 (s), 93.7 (s), 117.9 (d), 127.7 (s), 127.9 (s), 128.0 (d), 128.4 (d), 129.1 (d), 129.4 (d), 129.5 (d), 133.9 (s), 135.3 (d), 137.7 (s), 148.7 (s), 157.2 (s), 167.6 (s), 168.9 (s).

Anal. Calcd for $C_{25}H_{19}Cl_2NO_5S$: C, 58.15; H, 3.70; N, 2.71. Found: C, 58.45; H, 3.38; N, 2.91.

Dimethyl 3,5-dichloro-1-(4-methoxyphenyl)-8-(phenylthio)-11-oxa-4-azatricy-clo-[6.2.1. $0^{2,7}$]undeca-2,4,6-triene-9,10-dicarboxylate (134)



134

was prepared in a similar manner (modified conditions) from keto sulfoxide **127** (110 mg, 0.26 mmol) in 40% yield as a white solid: mp 164-166 °C.

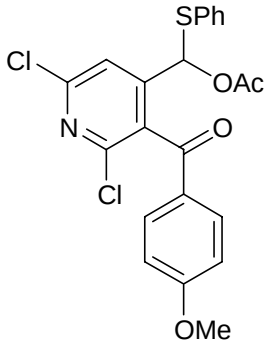
IR (KBr) 1743, 1596, 1339, 1246 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3.55 (s, 3H), 3.56 (s, 3H), 3.57 (d, 1H, *J* = 10.9 Hz), 3.89 (s, 3H), 4.13 (d, 1H, *J* = 10.9 Hz), 6.89-7.62 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 51.9 (q), 52.3 (q), 52.5 (d), 53.5 (d), 55.0 (q), 89.7 (s), 93.4 (s), 113.8 (d), 117.9 (d), 125.8 (s), 128.0 (s), 129.1 (d), 129.4 (d), 129.5 (d), 135.4 (d), 137.6 (s), 143.7 (s), 148.7 (s), 157.3 (s), 160.4 (s), 167.5 (s), 168.9 (s).

Anal. Calcd for $C_{26}H_{21}Cl_2NO_6S$: C, 57.15; H, 3.87; N, 2.56. Found: C, 56.98; H, 3.97; N, 2.43.

[2,6-Dichloro-3-(4-methoxybenzoyl)pyridin-4-yl](phenylthio) methyl acetate (136)



136

was obtained along with **127** via a Pummerer reaction of keto-sulfoxide **127** under Padwa's conditions as a white crystalline solid: mp 123-124 °C.

IR (KBr) 1763, 1661, 1573, 1569, 1318 cm^{-1}.

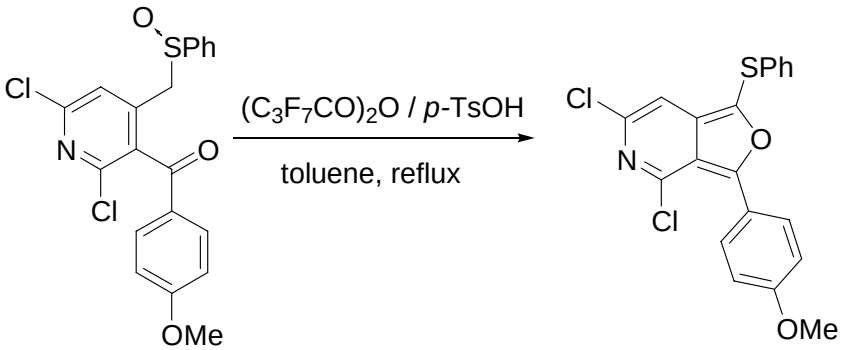
^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.98 (s, 3H), 3.88 (s, 3H), 6.75-7.91 (m, 11H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 20.6 (q), 55.5 (q), 77.4 (d), 114.2 (d), 120.6 (d), 128.8 (s), 129.2 (d), 129.5 (d), 129.9 (s), 130.7 (s), 132.3 (d), 134.6 (d), 147.2 (s), 149.7 (s), 150.7 (s), 164.8 (s), 168.3 (s), 189.9 (s).

LCMS *m*/*z* (rel intensity) 462 ($[M + H]^+$, 8), 402 ($[M - OAc]^+$, 100), 292 ($[M - OAc-PhSH]^+$, 71).

Anal. Calcd for $C_{22}H_{17}Cl_2NO_4S$: C, 57.15; H, 3.70; N, 3.02. Found: C, 57.29; H, 3.58; N, 2.97.

4,6-dichloro-3-(4-methoxyphenyl)-1-(phenylthio)furo[3,4-*c*]pyridine (**131**)



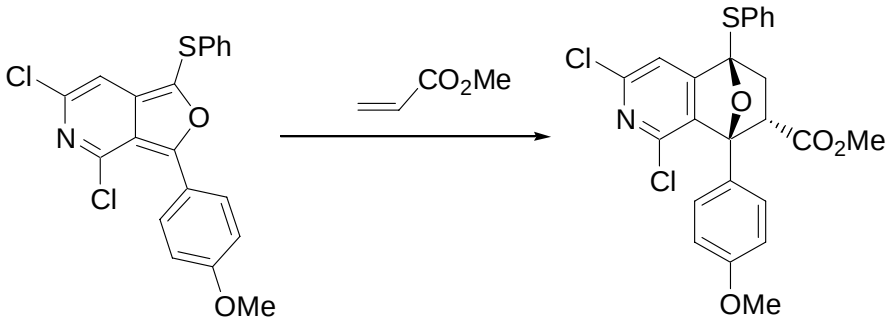
127 **131**

To a mixture of heptafluorobutyric anhydride (0.47 mL, 1.9 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 5 mL of toluene heated at reflux was added a toluene solution of keto-sulfoxide **127** (80 mg, 0.19 mmol) over a period of 10 min under argon atmosphere. The bright yellow mixture was allowed to reflux for an additional 1h, concentrated under reduced pressure, and purified by chromatography (EtOAc:petroleum ether 5:95) quickly. The intermediate 4,6-dichloro-3-(4-methoxyphenyl)-1-(phenylthio)furo[3,4-*c*]pyridine (**131**) (40 mg, 52% yield) was obtained as a yellow oil.

IR ($CDCl_3$) 1604, 1508, 1259 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.01 (d, 2H, *J* = 8.8 Hz), 7.11-7.25 (m, 5H), 7.31 (s, 1H), 7.75 (d, 2H, *J* = 8.8 Hz).

Methyl 3,5-dichloro-1-(4-methoxyphenyl)-8-(phenylthio)-11-oxa-4-azatricyclo [6.2.1.0^{2,7}]- undeca-2,4,6-triene-10-carboxylate (140)



131 **140**

To a well-stirred toluene (5 mL) solution of **131** (40 mg, 0.099 mmol) was added methyl acrylate (0.068 mL, 0.76 mmol) and the mixture was heated at reflux for 1 h under argon. The resulting yellow solution was triturated with 5 mL of ether, washed with H_2O, and concentrated under reduced pressure. Purification of the crude product by preparative layer chromatography yielded a mixture of two isomers (18 mg, 36% yield) which on crystallization gave **140** as the major isomer: mp 117-119 °C.

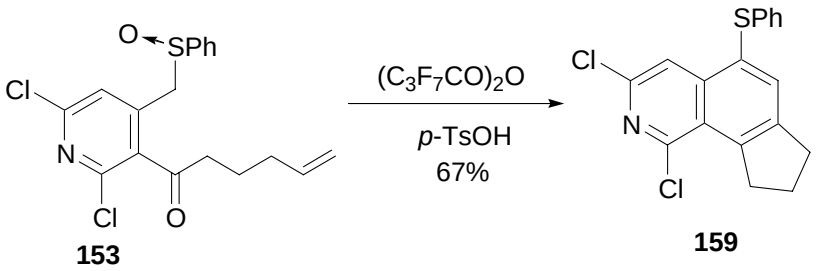
IR (KBr) 1736, 1575, 1320, 1220 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.12 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.2 Hz), 2.58 (dd, 1H, J_1 = 12.2 Hz, J_2 = 10.2 Hz), 3.57 (s, 3H), 3.86 (s, 3H), 3.91 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.2 Hz), 6.91-7.10 (m, 2H), 7.16 (s, 1H), 7.25-7.39 (m, 3H), 7.51-7.68 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 39.8 (t), 47.7 (d), 52.4 (q), 55.3 (q), 90.4 (s), 92.8 (s), 113.8 (d), 114.9 (d), 125.9 (s), 129.0 (d), 129.1 (d), 129.3 (s), 130.0 (d), 134.2 (d), 136.7 (s), 143.7 (s), 149.6 (s), 160.0 (s), 160.4 (s), 170.9 (s).

When the reaction was conducted in one pot (cf. modified conditions), the overall yield of products **140** and **141** was higher (46%).

1,3-Dichloro-5-(phenylthio)-8,9-dihydro-7*H*-cyclopenta[*h*]isoquinoline (159)



153 **159**

was prepared in a similar manner (modified conditions) from keto-sulfoxide **153** (50 mg, 0.13 mmol) in 67% yield as a white crystalline solid: mp 109-110 °C.

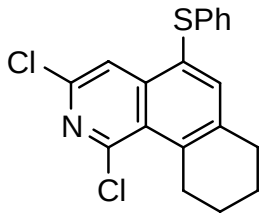
IR (KBr) 1577, 1538, 1278, 1177 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (quint, 2H, *J* = 7.6 Hz), 3.03 (t, 2H, *J* = 7.7 Hz), 3.74 (t, 2H, *J* = 7.5 Hz), 7.01-7.45 (m, 5H), 7.78 (s, 1H), 8.20 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3 (t), 33.3 (t), 36.4 (t), 118.4 (d), 124.9 (s), 126.8 (d), 128.1 (s), 129.2 (d), 129.3 (d), 134.3 (s), 135.5 (d), 140.3 (s), 141.5 (s), 142.7 (s), 146.0 (s), 149.9 (s).

Anal. Calcd for $C_{18}H_{13}Cl_2NS$: C, 62.42; H, 3.78; N, 4.04. Found: C, 62.24; H, 3.55; N, 4.29.

1,3-Dichloro-5-(phenylthio)-7,8,9,10-tetrahydrobenzo-[*h*]isoquinoline (160)



160

was prepared from keto sulfoxide **154** (40 mg, 0.1 mmol) by similar methodology in 56% yield as a white crystalline solid: mp 89-91 °C.

IR (KBr) 1574, 1539, 1333, 1112, 1025 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 1.78-1.98 (m, 4H), 2.79-3.05 (m, 2H), 3.45-3.63 (m, 2H), 7.01-7.41 (m, 5H), 7.60 (s, 1H), 8.17 (s, 1H).

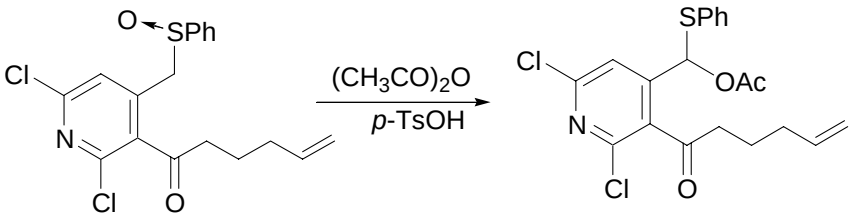
^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.7 (t), 23.2 (t), 31.1 (t), 31.2 (t), 118.3 (d), 126.8 (d), 127.3 (s), 127.9 (s), 129.0 (d), 129.4 (d), 135.7 (s), 136.1 (s), 138.5 (s), 140.8 (d), 141.0 (s), 142.8 (s) 149.0 (s).

FAB MS *m/z* (rel intensity) 360 ($[M + H]^+$, 21), 273 (3), 235 (6), 165 (5).

HRMS (FAB) calcd for $C_{19}H_{16}Cl_2NS$ $(M + H)^+$ *m/z* 360.0380, found 360.0381.

Anal. Calcd for $C_{19}H_{15}Cl_2NS$: C, 63.34; H, 4.19; N, 3.88. Found: C, 62.98; H, 4.35; N, 4.29.

(2,6-Dichloro-3-hex-5-enoylpyridin-4-yl)(phenylthio)methyl acetate (161)



153 **161**

A mixture containing acetic anhydride (0.05 ml, 0.5 mmol) and a catalytic amount of *p*-toluenesulfonic acid in dry toluene (5 mL) was heated at reflux under argon. To this mixture was added a toluene solution of keto-sulfoxide **153** (20 mg, 0.052 mmol) dropwise over a period of 10 min. After addition was complete the yellow mixture was heated at reflux for an additional 1 h. The reddish yellow solution was cooled and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was concentrated and purified by preparative layer chromatography gave 14 mg (63%) of **161** as.a colourless liquid.

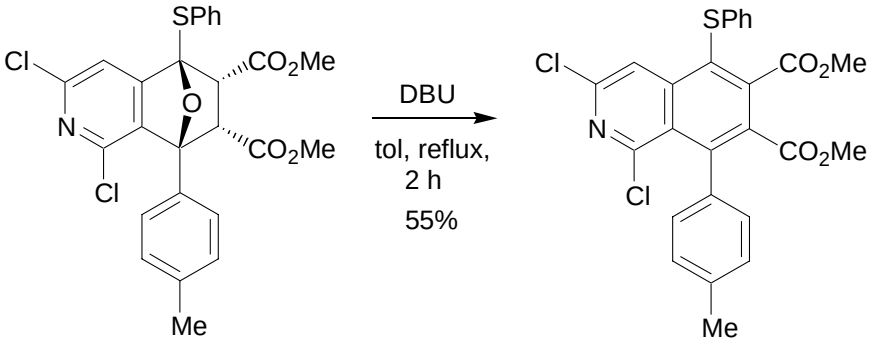
IR (CH_2Cl_2) 1756, 1701, 1572, 1015 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 1.78-1.1.98 (m, 2H), 2.12 (s, 3H), 2.02-2.24 (m, 2H), 2.91-3.08 (m, 2H), 4.91-5.09 (m, 2H), 5.62-5.91 (m, 1H), 6.85 (s, 1H), 7.02 (s, 1H), 7.31-7.48 (m, 5H).

^{13}C NMR (300 MHz, $CDCl_3$) δ20.9 (q), 22.3 (t), 32.8 (t), 43.3 (t), 76.5 (d), 115.5 (t), 120.6 (d), 129.2 (s), 129.4 (d), 130.0 (d), 132.2 (s), 135.0 (d), 137.7 (d), 145.3 (s), 148.4 (s), 150.6 (s), 168.7 (s), 202.3 (s).

HRMS calcd for $C_{20}H_{20}Cl_2NO_3S$ $(M+ H)^+$ *m/z* 424.0541, found 424.0542.

Dimethyl 1,3-dichloro-8-(4-methylphenyl)-5-(phenylthio)isoquinoline-6,7-dicarboxylate (164)



133 **164**

To a stirred solution of oxa-bridged diester **133** (80 mg, 0.15 mmol) in 5 mL of toluene was added DBU (0.22 mL, 1.5 mmol) dropwise at room temperature. The mixture was heated at reflux for 1.5 h giving a reddish yellow solution, cooled, washed with 10% HCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (EtOAc:petroleum ether 10:90) gave 42 mg (55%) of **164** as a yellow crystalline solid: mp 160-161 °C.

IR (KBr) 1735, 1585, 1363, 1333, 1062 cm^{-1}.

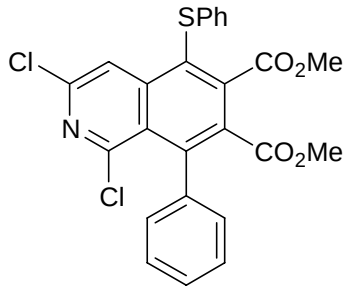
^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.44 (s, 3H), 3.47 (s, 3H), 3.87 (s, 3H), 7.08-7.40 (m, 9H), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.5 (q), 52.5 (q), 53.0 (q), 118.9 (d), 125.0 (s), 127.1 (d), 127.8 (s), 128.6 (d), 128.7 (d), 129.5 (d), 133.5 (s), 134.3 (s), 135.2 (s), 138.5 (s), 141.4 (s), 141.6 (s), 142.8 (s), 146.0 (s), 151.8 (s), 166.6 (s), 166.9 (s).

FAB MS *m/z* (rel intensity) 512 ($[M + H]^+$, 21), 480 ($[M - OCH_3]^+$, 9), 412 (2), 273 (3), 235 (6), 165 (5).

Anal. Calcd for $C_{26}H_{19}Cl_2NO_4S$: C, 60.95; H, 3.73; N, 2.73. Found: C, 60.92; H, 3.85; N, 2.89.

Dimethyl 1,3-dichloro-8-phenyl-5-(phenylthio)-isoquinoline-6,7-dicarboxylate (163)



163

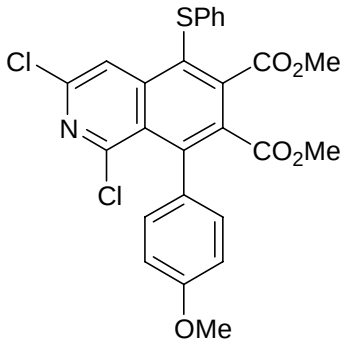
was prepared similarly by treatment of **132** (150 mg, 0.29 mmol) with DBU in 53% yield: mp 178-179 °C.

IR (KBr) 1737, 1584, 1375, 1316, 1062 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 3. 43 (s, 3H), 3.88 (s, 3H), 7.15-7.32 (m, 6H), 7.35-7.48 (m, 4H), 8.37 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 52.5 (q), 53.0 (q), 119.0 (d), 124.8 (s), 127.2 (d), 127.9 (d), 128.0 (s), 128.6 (d), 128.8 (d), 129.5 (d), 129.6 (d), 133.4 (s), 135.0 (s), 137.3 (s), 141.1 (s), 141.6 (s), 142.7 (s), 146.2 (s), 151.7 (s), 166.6 (s), 166.9 (s).

Dimethyl 1,3-dichloro-8-(4-methoxyphenyl)-5-(phenylthio)isoquinoline-6,7-dicarboxylate (165)



165

was prepared by similar treatment of **134** (60 mg, 0.11 mmol) with DBU in 45% yield as a white crystalline solid: mp 190-192 °C.

IR (KBr) 1740, 1554, 1365, 1332, 1062 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.87 (s, 6H), 6.91-7.01 (m, 2H), 7.12-7.34 (m, 7H), 8.38 (s, 1H).

Anal. Calcd for $C_{26}H_{19}Cl_2NO_5S$: C, 59.10; H, 3.62; N, 2.65. Found: C, 59.32; H, 3.59; N, 2.55.

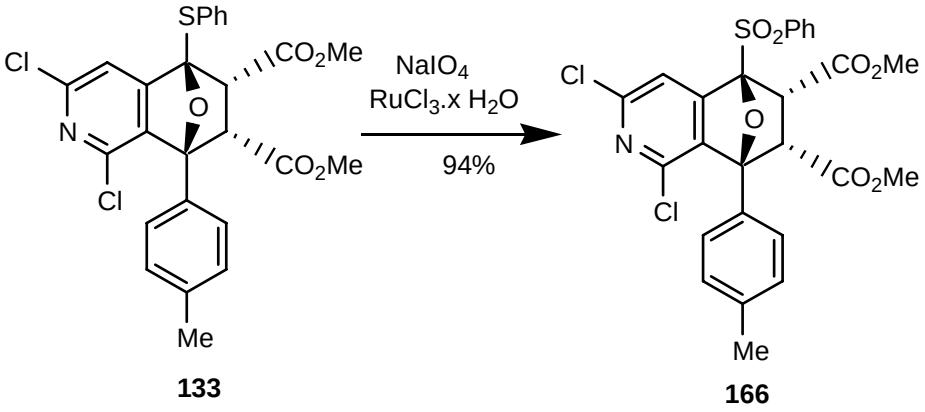
One pot synthesis of 165

A mixture containing heptafluorobutyric anhydride (0.25 mL, 1.01 mmol), dimethyl maleate (0.048 mL, 0.38 mmol), and a catalytic amount of *p*-toluenesulfonic acid in toluene (5 mL) was heated at reflux under argon. To this mixture was added keto-sulfoxide **127** (40 mg, 0.095 mmol) in dry toluene dropwise over a period of 10 min. After complete addition, the yellow mixture was heated at reflux for an additional 1 h. The reddish yellow solution was cooled to room temperature and then DBU (0.45 ml, 3.03 mmol) was added. The reaction mixture was heated to reflux for additional 1h. Then

the reaction mixture was cooled, washed with 10% HCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification (EtOAc:petroleum ether 10:90) gave 10 mg (20 % from **127**) of **165** as a white crystalline solid.

^{1}H NMR of the product is identical with the above.

Dimethyl 3,5-dichloro-1-(4-methylphenyl)-8-(phenylsulfonyl)-11-oxa-4-azatri-cyclo [6.2.1. 02,7]undeca-2,4,6-triene-9,10-dicarboxylate (166).



133 **166**

To a mixture of oxa-bridged diester **133** (140 mg, 0.264 mmol) and $NaIO_4$ (240 mg, 1.12 mmol) in a 10 mL mixture of CH_3CN, CCl_4, H_2O (1:1:3) was added a catalytic amount of $RuCl_3.xH_2O$. The solution was stirred at room temperature for 2 h and then diluted with 5 mL of CH_2Cl_2. The resulting two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude black residue was diluted with 20 mL of diethyl ether and filtered through a short column of silica gel, which on concentration gives 140 mg (94%) of **166** as a white crystalline solid: mp 202-203 °C.

IR (KBr) 1750, 1591, 1333, 1164 cm^{-1}.

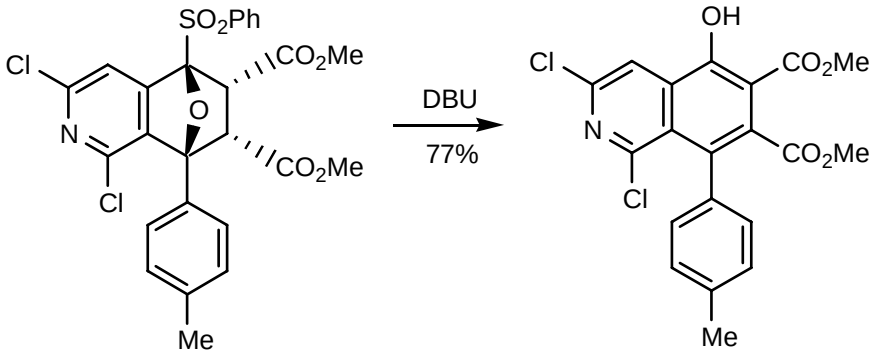
^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.58 (s, 3H), 3.66 (s, 3H), 4.21 (d, 1H, *J* = 11.2 Hz), 4.29 (d, 1H, *J* = 11.2 Hz), 7.12 (s, 4H), 7.51-7.99 (m, 5H), 7.93 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (q), 50.8 (d), 52.6 (q), 53.0 (d), 91.8 (s), 98.0 (s), 118.3 (d), 127.8 (d), 129.2 (d), 129.3 (d), 129.8 (s), 130.2 (d), 134.7 (s), 135.1 (d), 137.6 (s), 140.0 (s), 144.5 (s), 149.2 (s), 152.8 (s), 167.2 (s), 168.4 (s).

DCI-MS *m/z* (rel intensity) 579 ($[M + NH_4]^+$, 14), 562 ($[M + H]^+$, 100).

HRMS (FAB) calcd for $C_{26}H_{22}Cl_2NO_7S$ $(M+ H)^+$ *m/z* 562.0494, found 562.0507.

Dimethyl 1,3-dichloro-5-hydroxy-8-(4-methylphenyl)-isoquinoline-6,7-dicarboxylate (167)



166 **167**

To a stirred solution of sulfone **166** (140 mg, 0.25 mmol) in 10 mL of toluene was added DBU (0.075 mL, 0.5 mmol) at room temperature and the mixture was then heated to reflux for 1 h under argon. The reddish yellow solution was washed with 10% HCl, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue

on chromatographic purification (EtOAc:petroleum ether 30:70) gave 80 mg (77%) of **167** as a white crystalline solid: mp 209 °C.

IR (KBr) 3441, 3018, 1732, 1612, 1558, 1199 cm^{-1}.

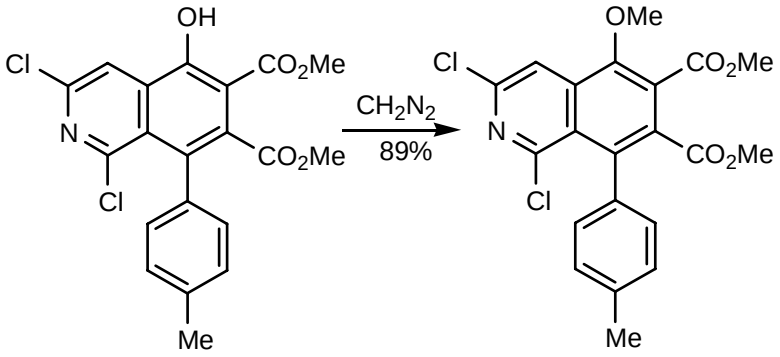
^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.47 (s, 3H), 3.97 (s, 3H), 7.08 (d, 2H, *J* = 8.1 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 8.31 (s, 1H), 12.42 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (q), 51.9 (q), 53.6 (q), 106.0 (s), 116.2 (d), 126.4 (s), 128.2 (d), 128.7 (s), 130.8 (d), 133.4 (s), 134.3 (s), 137.9 (s), 143.7 (s), 144.4 (s), 150.4 (s), 158.6 (s), 167.7 (s), 169.3 (s).

DCI-MS *m/z* (rel intensity) 437 ($[M + NH_4]^+$, 7), 420 ($[M + H]^+$, 100).

HRMS (FAB) calcd for $C_{20}H_{16}Cl_2NO_5$ $(M + H)^+$ *m/z* 420.0406, found 420.0410.

Dimethyl 1,3-Dichloro-5-methoxy-8-(4-methylphenyl)-isoquinoline-6,7-dicarboxylate (168)



167 **168**

Diazomethane generated from *N*-nitroso *N*-methyl urea (236 mg, 2.29 mmol) and 40% aqueous KOH in diethyl ether was added to 120 mg (0.28 mmol) of **167** at 0 °C.

After vigorous hand stirring the ice bath was removed and the reaction mixture was left at room temperature overnight. Ether was removed under reduced pressure and the residue on chromatographic purification (EtOAc:petroleum ether 20:80) gave 110 mg (89%) of **168** as a white solid: mp 135-137 °C.

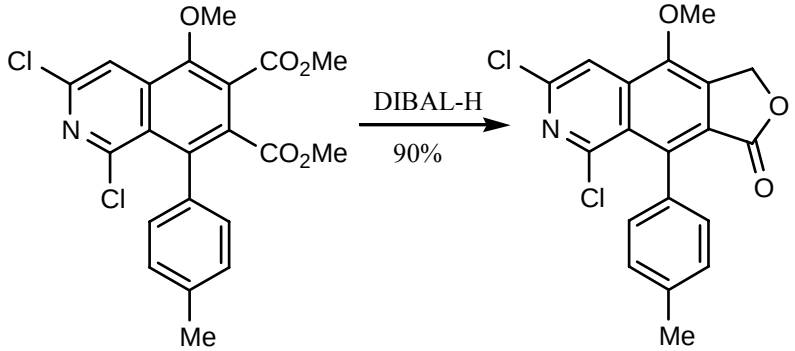
IR (KBr) 1740, 1560, 1338, 1208 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3) δ 2.41 (s, 3H), 3.44 (s, 3H), 3.93 (s, 3H), 4.07 (s, 3H), 7.09 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 8.03 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3) δ 21.4 (q), 52.2 (q), 53.0 (q), 63.7 (q), 115.0 (d), 124.1 (s), 125.4 (s), 128.3 (d), 130.0 (d), 134.1 (s), 134.4 (s), 134.6 (s), 136.5 (s), 137.9 (s), 144.9 (s), 151.3 (s), 153.0 (s), 165.4 (s), 167.0 (s).

Anal. Calcd for $C_{21}H_{17}Cl_2NO_5$: C, 58.09; H, 3.94; N, 3.22. Found: C, 58.19; H, 3.89; N, 3.41.

5,7-Dichloro-9-methoxy-4-(4-methylphenyl)furo[3,4-*g*]-isoquinolin-3(1*H*)-one (169)



168 **169**

To a stirred solution of **168** (50 mg, 0.11 mmol) in 10 mL of CH_2Cl_2 cooled to -78 °C was added 0.25 mL of DIBAL-H (1.0 M solution in toluene) dropwise under argon. The resulting mixture was stirred for 30 min at the same temperature and then allowed to warm to 0 °C. The reaction mixture was quenched with 2 mL of saturated aqueous NH_4Cl solution and stirred for 30 min, then it was acidified with 20 % HCl and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduce pressure and on preparative layer chromatographic purification gave 40 mg (90%) of **169** as a white crystalline solid: mp 252-254 °C.

IR (KBr) 1779, 1573, 1460, 1333 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.19 (s, 3H), 5.59 (s, 2H), 7.01-7.35 (m, 4H), 8.14 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5 (q), 59.9 (q), 65.8 (t), 114.8 (d), 124.5 (s), 125.7 (s), 128.5 (d), 129.0 (s), 129.3 (d), 131.7 (s), 137.0 (s), 137.7 (s), 138.2 (s), 145.3 (s), 147.8 (s), 152.5 (s), 167.3 (s).

FAB MS *m/z* (rel intensity) 374 ($[M + H]^+$, 8), 329 ($[M - CO_2]^+$, 3) 273 (6), 242 (5), 165 (6).

HRMS (FAB) calcd for $C_{19}H_{14}Cl_2NO_3$ $(M + H)^+$ *m/z* 374.0351, found 374.0351.

Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$: C, 60.98; H, 3.49; N, 3.74. Found: C, 60.71; H, 3.32; N, 3.85.

7. References

1. For reviews see: (a) Friedrichsen, W., *Adv*. *Heterocycl*. *Chem*. **1999**, *73*, 1. (b) Traulsen, T.; Friedrichsen, W. *Targets in Heterocyclic Systems*: *chemistry and properties*, Vol. 2, Societa Chimica Italiana, **1998**, pp. 59. (c) Wege, D. *Aust. J. Chem*., **1998**, *51*, 1. (d) Peters, O.; Friedrichsen, W. *Trends heterocyclic chemistry*, **1995**, *4*, 217. (e) Friedrichsen, W. In *Methoden der organischen chemie (Houben-Weyl)*, Vol. E6b1, Kreher, R., Ed., Thieme: 1**994**; Vol. E6b1, pp.163. (f) Rickborn, B. In *Advances in theoretically interesting molecules*, Vol. 1, Thummel, R. P, Ed., JAI Press: Greenwich, CT, **1989**, pp. 1-134. (g) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (h) Wiersum, U. E. *Aldrichimica Acta*, **1981**, *14*, 53. (i) Friedrichsen, W. *Adv*. *Heterocyclc*. *Chem*. **1980**, *26*,135. (j) Haddadin, M. J. *Heterocycles* **1978**, *9*, 865.
2. Padwa, A. *Chem*. *Commun*. **1998**, 1417.
3. For a review on heteroisobenzofurans, see: Basak, S.; Ghosh S. K.; Sarkar T. K. *J. Indian Inst*. *Sci*., **2001**, *81*, 431.
4. Moskalev, N. V.; Gribble, G. W.; *Tetrahedron Lett*. **2000**, *43*, 197.
5. (a) Wiersum, U. E.; Eldred, C. D. *Tetrahedron Lett*. **1977**, 1741. (b) Muller, P.; Schaller, J.-P. *Tetrahedron Lett.* **1989**, *30*, 1507.
6. (a) Eberbach, W.; Fritz, H.; Laber, N. *Angew. Chem. Int. Ed. Engl*. **1988**, *27*, 568. (b) Eberbach, W.; Laber, N.; Bussenius, J.; Fritz, H.; Ribs, G. *Chem. Ber.* **1993**, *126*, 975. (c) Bussenius, J.; Keller, M.; Eberbach, W. *Liebigs Ann.* **1995**, 1503.
7. Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem*. **1992**, *57*, 5878.

8. (a) Friedrichsen, W.; Schöoning, A. *Heterocycles* **1986**, *24*, 307. (b) Schöoning, A.; Debaerdemaeker, T.; Zander, M.; Friedrichsen, W. *Chem. Ber.* **1989**, *122*, 1119.

9. Aβmann, L.; Palm, L.; Zander, M.; Friedrichsen, W. *Chem. Ber.* **1991**, *124*, 2481.

10. Kappe, C. O.; Padwa, A. *J. Org. Chem*. **1996**, *61*, 6166.

11. Abdou, W. M.; Kamel, A. A. *Tetrahedron* **2000**, *56*, 7573.

12. Miki, Y.; Hachiken, H. *Synlett* **1993**, 333.

13. (a)) Schöoning, A.; Friedrichsen, W. *Liebigs Ann.* **1989**, 405. (b) Schöoning, A.; Friedrichsen, W. *Z. Naturforsch B* **1989**, *44*, 825.

14. For a review on heterolignans, see: Ramos, A. C.; deClairac, R. P.-L.; Medarde, M. *Heterocycles* **1999**, *51*, 1443.

15. (a) Canel, C.; Moraes, R. M.; Dayan, F. E.; Ferreira, D. *Phytochemistry* **2000**, *54*, 115. (b) Imbert, T. *Biochimie* **1998**, *80*, 207.

16. (a) Stahelin, H.; von Wartburg, A. *Cancer Res.* **1991**, *51*, 5. (b) Hande, K. R. *Eur. J. Cancer* **1998**, *34*, 1514.

17. For recent reviews on pharmacological activity see: (a) Damayanthi, Y; Lawn, J.-W. *Current Med. Chem* **1998**, *5*, 205. (b) Sackett, D.-L. *Pharmac Ther.* **1993**, *59*, 163. (c) Wood, K. W.; Cornwell, W. D.; Jackson, J. R. *Curr. Opinion Pharm*. **2001**, *1*, 370.

18. Tratrat, C.; Giorgi-Renault, S.; Husson, H. -P. *Org. Lett.* 2**002**, *4*, 3187. (b) Hitotsuyanagi, Y.; Fukuyo, M.; Tsuda, K.; Kobayashi, M.; Ozeki, A.; Itokawa, H.; Takeya, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 315. (c) Marcantoni, E.; Petrini, M.; Profeta, R. *Tetrahedron Lett.* **2004**, *45*, 2133.

19. For a review see: Desbène, S.; Giorgi-Renault, S. *Curr. Med. Chem.- Anti-Cancer Agents* **2002**, *2*, 71.

20. Pearce, H.; Bach, N.; Cramer, T.; Danks, M.; Grindy, G.; Katterjohn, S.; Rizen, S.; Back; W. *Cancer Res.* **1990**, *31*, 441.

21. Leteurtre, F.; Madalengoitia, J.; Orr, A.; Guzi, T. J.; Lehnert, E. ; Macdonald, T. ; Lehnert, E. ; Macdonald, T.; Pommier, Y. *Cancer Res.* **1992**, *52*, 4478.

22. Guillou, C. C.-L.; Rémuzon, P.; Bouzard, D.; Quirion, J. -C.; Giorgi-Renault, S.; Husson, H.-P. *Tetrahedron*, **1998**, *54*, 83.

23. Ding, H.; Lu, W.; Yang, L.; Zhang, Q.; Zhou, C.; Wu, X.; Boudoin, O.; Cai, J.; Gueritte, F.; Zhao, Y. *Chemistry & Biodiversity* **2005**, *2*, 1217.

24. Baba, A.; Kawamura, N.; Makino, H.; Ohta, Y.; Taketomi, S.; Sohda, T. *J. Med. Chem.* **1996**, *39*, 5176.

25. Iwao, M.; Inoue, H.; Kuraishi, T. *Chem*. *Lett*. **1984**, 1263.

26. a) Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Nishitani, T.; Kondo, K.; Iwasaki, T. *J. Org*. *Chem*. **1994**, *59*, 7353; b) Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Kondo, K; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1635.

27. Iwasaki, T.; Kondo, K., Kuroda, T.; Moritani, Y.; Yamagata, S.; Sugiura, M.; Kikkawa, H.; Kaminuma, O.; Ikezawa, K. *J*. *Med*. *Chem*., **1996**, *39*, 2696.

28. Sugahara, M.; Moritani, Y.; Kuroda, T.; Kondo, K.; Ukita, T. *J. Chem*. *Soc*. *Perkin Trans*. *1*. **2002**, 768.

29. Arduengo III, A. J.; Harlow, R. L.; Kline, M. *J*. *Am*. *Chem*. *Soc*. **1991**, *113*, 361.

30. Fink, M. J.; Michalczyk, M. J.; Haller, K. J.; West, R.; Michl, J. *J. Chem. Soc. Chem. Comm.* **1983**, 1010.

31. Trahanovsky, W. S.; Huang, Y. J.; Leung, M.-K. *J. Org. Chem.* **1994**, *59*, 2594.

32. (a) Fieser, L. F.; Haddadin, M. J.; *J. Am. Chem. Soc.* **1964**, *86*, 2081. (b) Fieser, L. F.; Haddadin, M. J.; *Can. J. Chem.* **1965**, *43*, 1599.

33. Petracek, F. J.; Sugisaka, N.; Klohs, M. W.; Parker, R. G. Bordner, J.; Roberts, J. D. *Tetrahedron Lett.* **1970**, 707.

34. Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088.

35. (a) Sarkar, T. K.; Ghosh, S. K.; Nandy, S. K.; Chow, T. J. *Tetrahedron Lett.* **1999**, *40*, 397. (b) Sarkar, T. K.; Ghosh S. K.; Chow, T. J. *J. Org. Chem.* **2000**, *65*, 3111.

36. (a) Sarkar, T. K.; Basak, S.; Ghosh S. K. *Tetrahedron Lett.* **2000**, *41*, 759. (b) Sarkar, T. K.; Basak, S.; Slanina, Z.; Chow, T. J. *J. Org. Chem.* **2003**, *68*, 4206.

37. (a) Padwa, A.; Cochran, J. E.; Kappe, C. O. *J. Org. Chem.* **1996**, *61*, 3706. (b) For a recent review on Pummerer reaction, see: Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

38. For a review on the Pummerer reaction and different triggering methods, see: DeLucchi, O.; Miotti, U.; Modena, G. Organic Reactions; Paquette, L. A., Ed.; John Wiely: 1991; Chapter 3, pp157-184.

39. Private communication from Prof. T. Gallagher, University of Bristol, UK.

40. Usman. A.; Sarkar, T. K.; Panda, N.; Fun, H. K. *Act. Cryst.* **2002**, *E58*, 1404.

41. Schöening, A.; Debaerdemaeker, T.; Zander, M.; Friedrichsen, W. *Chem. Ber.* **1989**, *122*, 1119.

42. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976.

43. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, N.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

44. Pindur, U.; Haber, M.Sattler, K. *J. Chem. Edu.* **1993**, *70*, 263.

45. a) Ware, B. D., Palmer, B. D., Wilson, W. R., Denny, W. A. *J. Med. Chem.*, **1993**, *36*, 1839. b) *Prodrugs in Cancer Chemotherapy*, ed. H. Burgard, Elsevier, 1985 and references there in.

46. Nicolaou, K.C. *Chem. Br.* **1994**, *30*, 33.

47. Shepherd, T. A.; Jungheim, L. N.; Meyer, D. L.; Starling, J. J. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 21.

48. Bailey, J. H.; Coulter, C. V.; Pratt, A. J.; Robinson, W. T. *J. Chem. Soc. Perkin Trans. 1* **1995**. 589.

49. Fun, H. K.; Usman, A.; Razak, I. A.; Chantrapromma, S.; Sarkar, T. K.; Basak, S., Panda, N. *Acta. Cryst.* **2002**, *E58*, 215.

50. Arnold, B. J.; Mellows, S.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1266.

51. Compaigne, E.; Homfeld, E. *J. Heterocycl. Chem.* **1979**, *16*, 1321.

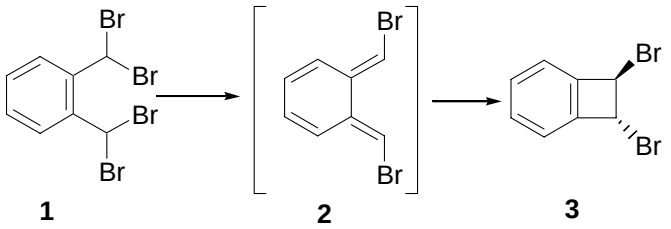
Chapter 2

A Formal Imine-Tautomerisation Route for the Generation and Trapping of Pyridine *o*-Quinodimethanes: Synthesis of Conformationally Restricted Analogues of Nicotine

1. Introduction

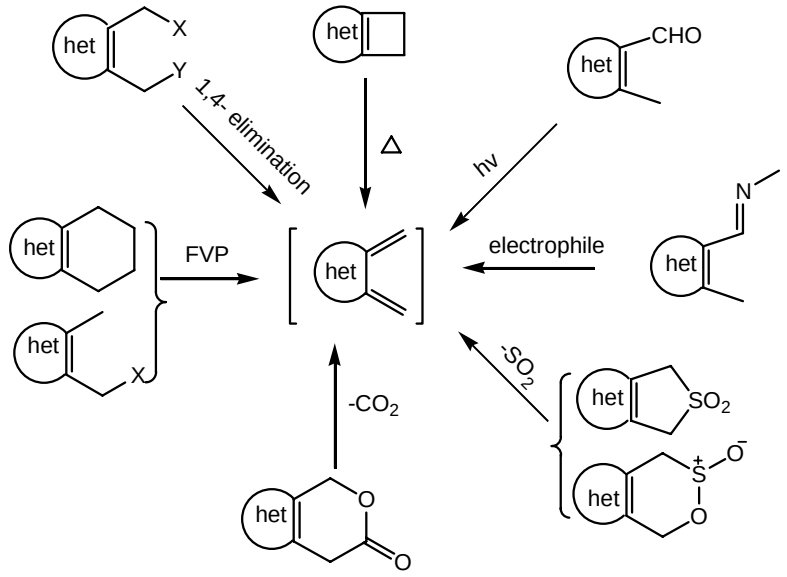
In 1957, Cava and Napier[1] first reported the generation of *o*-quinodimethane **2** as a reaction intermediate in the conversion of α,α,α′,α′- tetrabromo-*o*-xylene (**1**) to trans-1,2-dibromobenzocyclobutene (**3**) (Scheme 1). Since then, many methods for the generation of *o*-quinodimethanes have been developed and their characterization, structure, and chemical reactivity have been thoroughly studied.[2]

Scheme 1



In contrast, and in spite of their considerable potential in synthesis, heterocyclic analogues of *o*-quinodimethanes have received much less attention. However, in the last 15 years or so this situation has changed considerably and the ground rules for producing and handling such species have become much clearer. [2b, 3] The methods used to prepare hetero-*o*-quinodimethanes are summarized in Scheme 2.

Scheme 2



In the previous chapter, we have discussed our progress on the generation and trapping of furopyridines towards the synthesis of some biologically important molecules. One of the successful ventures in this regard has been the intramolecular Diels-Alder trapping of furopyridines which provides a novel route for the synthesis of conformationally restricted anabasines. However, this route failed for the synthesis of conformationally restricted nicotines. This failure prompted Sarkar et al. from this laboratory to develop an alternative route *via the generation and trapping of pyridine o-quinodimethanes* for the synthesis of conformationally restricted nicotines and to study their pharmacological activities.

In the last several decades, pharmacologists and chemists have focused an immense amount of research on the nicotinic receptor. At this juncture an overview on nicotinic acetylcholine receptors, the various nicotinic ligands with emphasis on

conformationally restricted nicotines and pharmacophoric models is presented here as it is relevant to this chapter.

1.1. Nicotinic acetylcholine receptors (nAChRs)

Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand gated ion channels found in the central and peripheral nervous systems that regulate synaptic activity.[4] nAChRs are a key target in drug discovery for a number of diseases, including Alzheimer's and Parkinson's disease, and have been widely discussed and investigated.[5]

The nicotinic acetylcholine receptors (nAChRs) have a pentameric structure and are composed of subunits that have distinct and overlapping expression patterns in subsets of neurons.[6, 7] Figure 1 illustrates a cross-section of cell membrane and pentameric nAChRs that protrude through the membrane. From the cross section of the

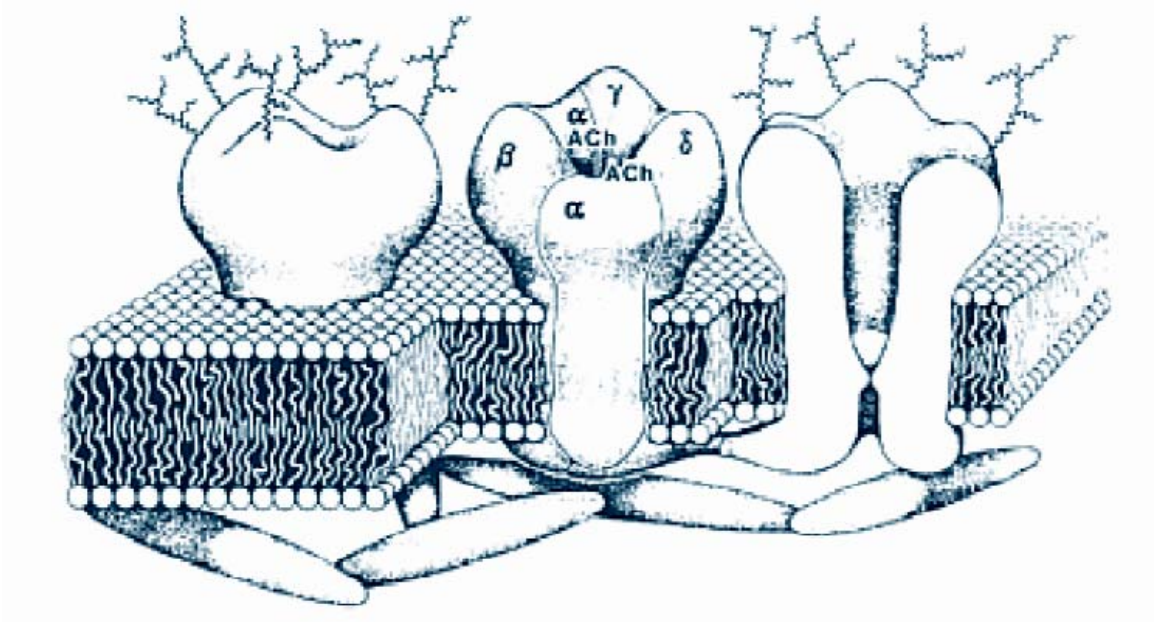


Figure 1

receptor one can see the ion channel pore in the closed state. Nicotine/acetylcholine binds to the receptor and opens the ion channel pore which affects the membrane potential and probability of depolarization.

Biochemical and molecular studies show that neuronal nicotinic acetylcholine receptors generally appear to consist of only two types of subunits — ligand binding α subunit (characterized by the presence of a pair of adjacent cysteine residues close to the acetylcholine binding site in the N-terminal domain) and structural β subunits (compared to the muscle nAChR which is comprised of four different subunits, α, β, δ and ε or γ).[6] The neuronal nicotinic acetylcholine receptors are generally believed to have a stoichiometry of two α subunits and three β subunits. Genes that are similar in sequence to the genes encoding the subunits of nicotinic acetylcholine receptors (nAChRs) at the neuromuscular junction (muscle) encode the subunits of neuronal nAChRs. To date, nine neuronal nAChR α gene (α2-α10) and three nAChR β genes (β2 – β4) have been cloned.[7, 8] These neuronal nAChR genes could generate a vast number of pentameric combinations of the receptor. Homo-oligomeric receptors can be assembled from α7, α8 or α9 subunits; combining α7 and α8 could generate hetero-oligomeric receptors (Fig. 2).[9]

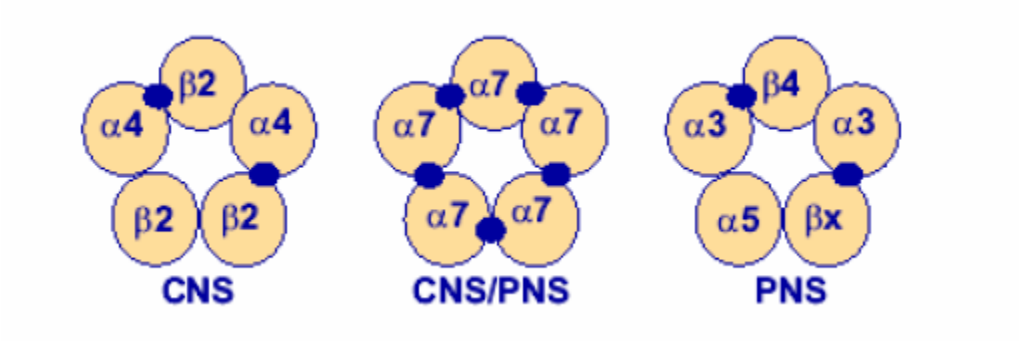


Figure 2. Major nAChR subtypes present in the central nervous system (CNS) and peripheral nervous system (PNS). Black circles represent putative agonist binding sites at subunit interfaces.

nAChR subtypes are found in different locations of the central and peripheral nervous system and have been assigned different pharmacological functions. For instance, the α4β2 and α4β4 subtypes appear to play a role in cognition, neurodegeneration, pain, anxiety, and depression; the α3β2 subtype plays a role in dopamine release and Parkinson's disease; the α7 plays a role in GABA release; the α9 plays a role in auditory function and development; and the α3β4 plays a role in norepinephrine release and cardiovascular and gastrointestinal action.[7d] Recent clinical studies have indicated potential efficacy of nicotine in the treatment of depression and normalization of auditory gating deficit in schizophrenic patients. Studies in animals and humans have shown consistent improvements in sustained attention. Deficits in attention are prevalent in ageing and in early stages of Alzheimer's disease (AD) as well as in Attention Deficit Hyperactivity Disorder (ADHD). *Thus, the therapeutic potential of nAChR agonists, such as nicotine, in Alzheimer's, Parkinson's disease, Tourette's syndrome, and pain is being recognized.*[10-15]

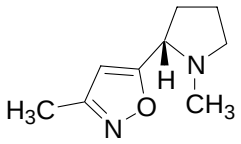
1.2. Nicotinic ligands and their synthesis

Critical limitations for the potential use of nicotine as a therapeutic are peripheral side effects that are due to the non-selective profile of nicotine. The side effects are observed in the gastrointestinal system, in the cardio-vascular system, and body temperature and nicotine is a relatively toxic compound that is reinforcing and likely

responsible for the addictive properties of tobacco.[16] Compounds that target specific subtypes in the CNS may not induce these side effects and yet retain the beneficial effects of nicotine. During the past 3 decades or so, vast efforts have been made to synthesize novel subtype selective nicotinic ligands [5, 11, 17-19] Based on the structure and conformation of nicotine two approaches are followed which are discussed here-in-after.

Pyridine and pyrrolidine modified analogues

Numerous pyridine and pyrrolidine modified analogues of nicotine were synthesized and their binding assays carried out.[5b, 18] Introduction of substituents at 3′, 4′, or 5′-positions of the pyrrolidine ring generally results in unfavourable binding. It may be mentioned here that one series of agonists from the Abbott Laboratories exemplified by ABT 418 (now available from Sigma-Aldrich) has entered clinical trials to treat the cognitive deficits associated with Alzhiemer disease.[20]



ABT- 418

Conformationally restricted analogues

During the past two decades or so a great stride has been made to probe the role of particular conformations on the pharmacological properties of important biologically active molecules such as amino acids,[21] peptides,[22] sugars,[23] nucleosides,[24] nucleotides,[23a, 25] nucleic acids,[26] vitamines,[27] raloxifene,[28] dihydropyrimidines,[29] etc. In almost all these studies the parent molecule is *modified in such a fashion that its original conformational*

mobility is severely limited to one particular conformation. For tobacco alkaloids nicotine (**4**) and anabasine (**5**) (Figure 3), the synthesis and evaluation of conformationally

Nicotine (**4**) Anabasine (**5**)

Figure 3

restricted analogues might provide informations on the steric and electronic requirements for optimal binding and functional potency, thus allowing development of a foundation for the rational design of new potent and selective neuronal nicotinic acetylcholine receptor ligands.[30] It should be pointed out that *the conformationally frozen nicotinic ligands can improve the affinity and specificity for a receptor primarily as a result of reducing the entropic loss upon binding.*

Chemists from far-flung laboratories have already generated an array of conformationally constrained nicotines and anabasines by tethering the two rings present in each of **4** and **5** with a short chain containing only carbon atoms or a combination of carbon and hetero atoms. A list of constrained nicotines and anabasines is shown in Figure 4.

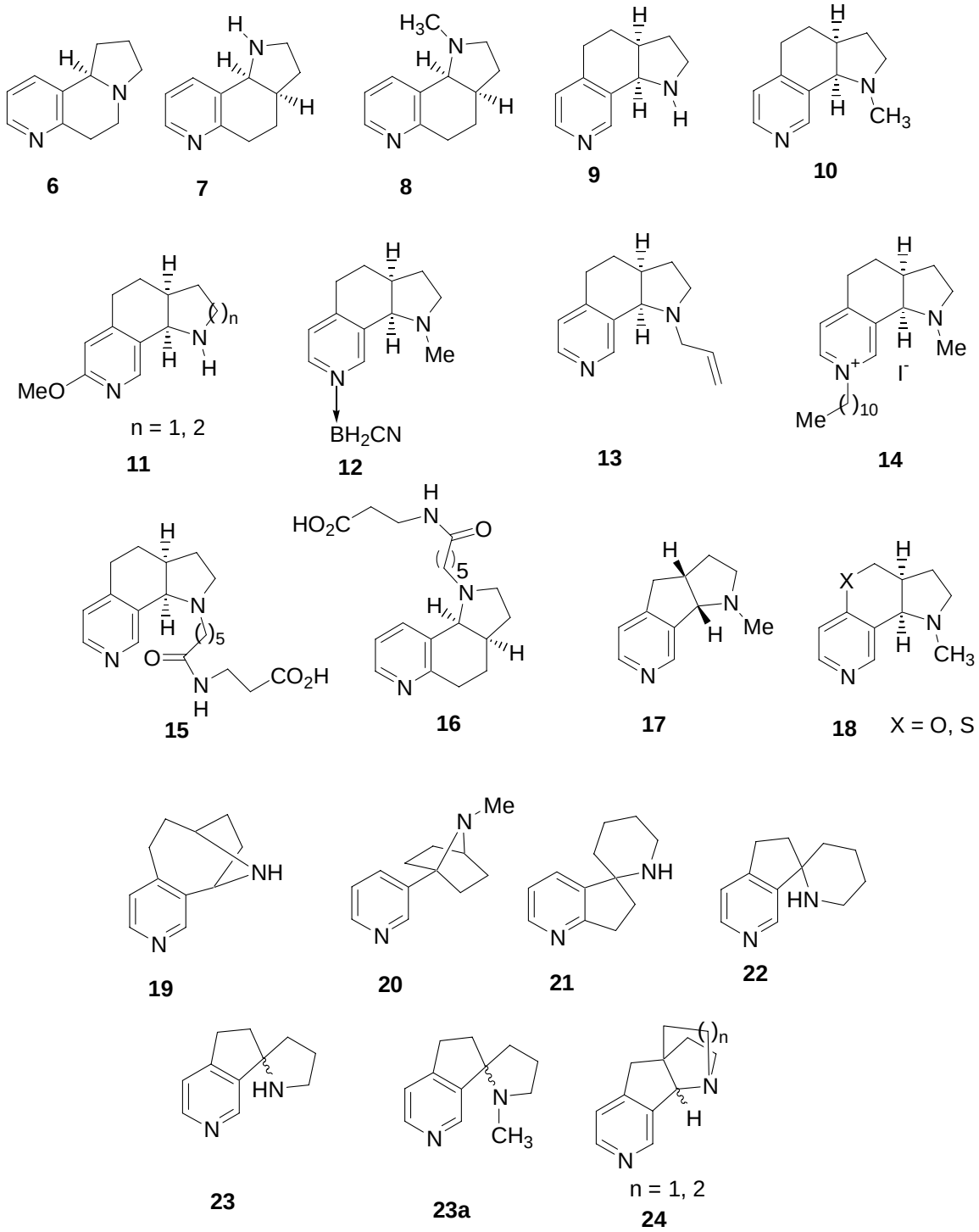
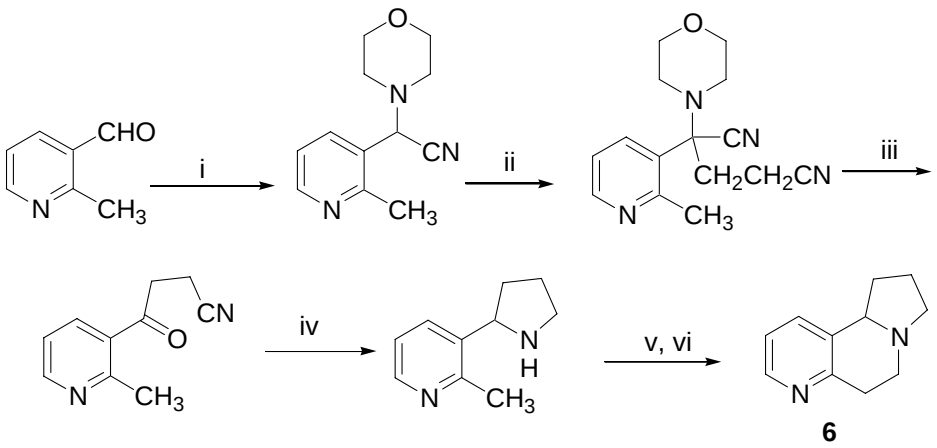


Figure 4

Various synthetic strategies were adopted for the synthesis of these types of ligands. In 1978 Catka and Leete[31] reported the synthesis of **6** as shown in Scheme 3; however, no biological assay of this compound was made. In 1983, Chavdarian et al.[32]

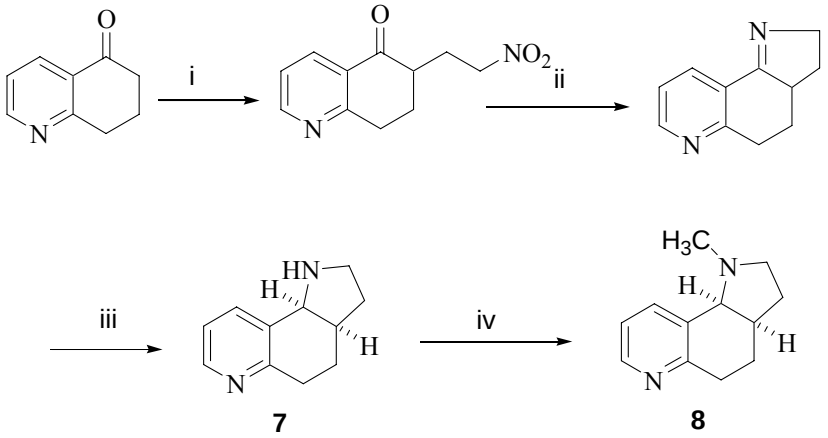
Scheme 3



Reagents: (i) morpholine, NaCN, $HClO_4$; (ii) $^tBuO^-K^+$, CH_2=CH-CH_2CN; (iii) H^+; (iv) Ra-Ni; (v) (a) n-BuLi, CO_2; (b) 1-ethyl-3(3-dimethylaminopropyl)carbodiimide; (vi) BH_3.THF.

reported the synthesis of **7** as well as the methylated analogue **8** (Scheme 4). In 1988,

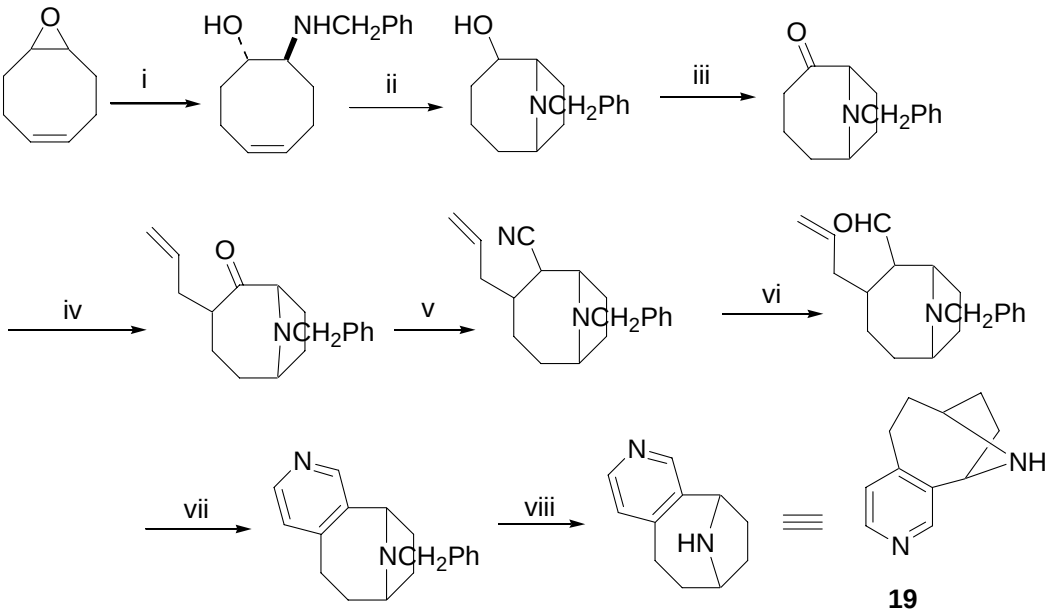
Scheme 4



Reagents: (i) (a) LDA, (b) nitroethylene; (ii) Ra Ni, H_2; (iii) $NaBH_3CN$; (iv) CH_2O, $NaBH_3CN$.

Kanne and co-workers[33] synthesized (Scheme 5) and bio-assayed the ligand **19**. This ligand has potent agonist activity in comparison to anatoxin-a (cf. Figure 6).

Scheme 5



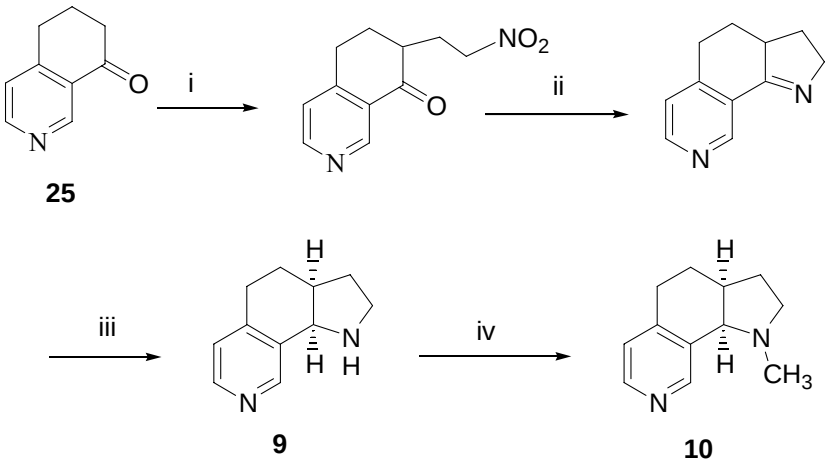
19

Reagents: (i) $PhCH_2NH_2$; (ii) $Hg(OAc)_2$, NaOH, $NaBH_4$; (iii) Jones oxidation; (iv) KH, Et_3B, allyl bromide, (v) TosMic, $^tBuO^-K^+$; (vi) DIBAL-H; (vii) (a) O_3, Me_2S; (b) $NH_2OH.HCl$, HOAC; (viii) H_2,-$Pd(OH)_2$/C, HCl.

In 1993, Glassco et al.[34] followed the Chavdharian's methodology[32] for the synthesis of **9** and **10** (Scheme 6). In this work the authors described an improved synthesis of the starting material **25** (Scheme 6). Much later (1998), Vernier et al.[35] reported on the synthesis and biological evaluation of a series of compounds displaying the structural fragment **9**; in particular, compound **11** (n = 1) (Figure 4) which selectively activates human recombinant α2β4 and α4β4 nAChRs has been shown to be active in animal models of Parkinson's disease and pain.[35] In 2003 using conformationally restricted

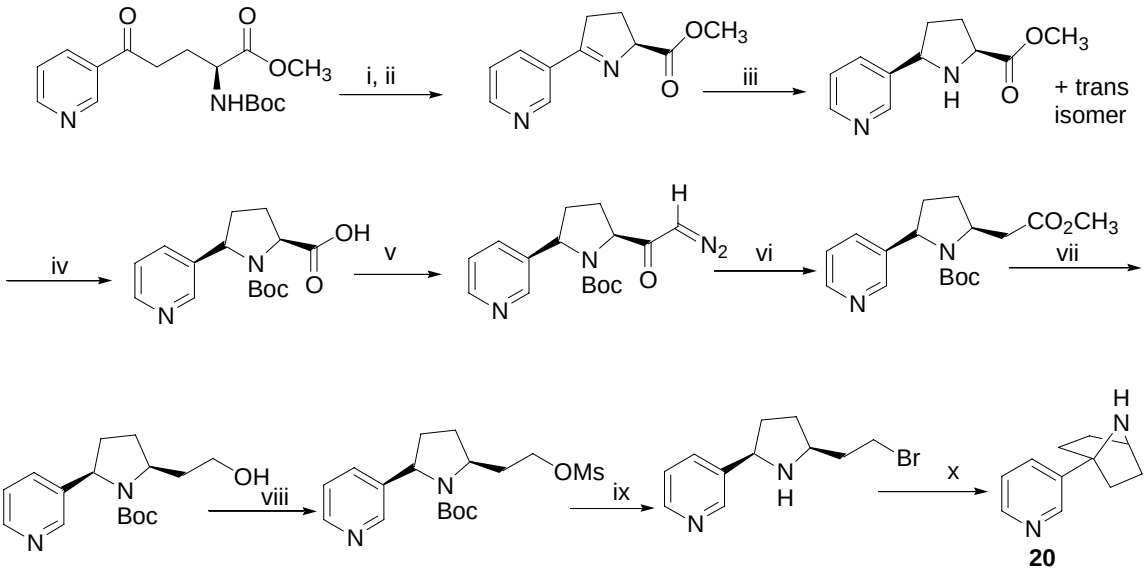
nicotines **15** and **16** (Figure 4) Janda et al. reported the impressive relationship between the conformational constraint of nicotine and its immunogenicity.[36] Conformationally constrained ligand **20** was synthesized by Xu et al.[37] in 1999 (Scheme 7).

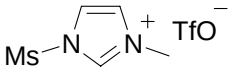
Scheme 6



Reagents: (i) (a) LDA, (b) nitroethylene; (ii) Ra Ni, H_2; (iii) $NaBH_3CN$; (iv) CH_2O, $NaBH_3CN$.

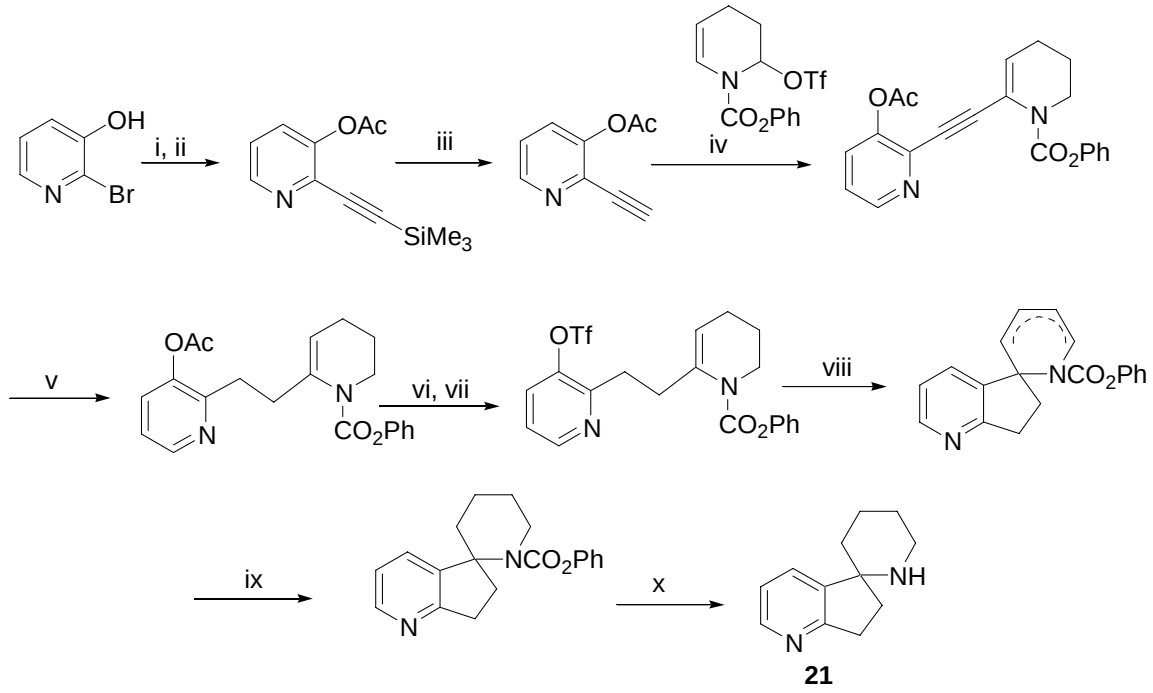
Scheme 7



Reagents: (i) HCl; (ii) $NaHCO_3$; (iii) $NaCNBH_3$; (iv) (a) $(Boc)_2O$, (b) $LiOH.H_2O$; (v) (a) EtOCOCl, Et_3N (b) CH_2N_2; (vi) $PhCO_2Ag$, Et_3N, MeOH; (vii) $CaCl_2$, $NaBH_4$; (viii)  , N-methylimidazole; (ix) LiBr; (x) (a) n-BuLi; (b) HCl.

Lindstrom et al.[38] also synthesized some conformationally constrained anabasines e.g. **21** via intramolecular Heck arylation reaction (Scheme 8). These ligands comprise a piperidine that is nearly perpendicular to the pyridine ring. Ullrich et al.[39] synthesized a set of novel conformationally constrained nicotines **23** and **24** (Scheme 9 and 10). The racemates **23** and **24** were resolved and the ability of the individual enantiomers were evaluated to displace [^{3}H]-cytisine in a rat forebrain preparation and compared with (-)-nicotine. The compound (+)-**23b** showed not only high binding affinity but also

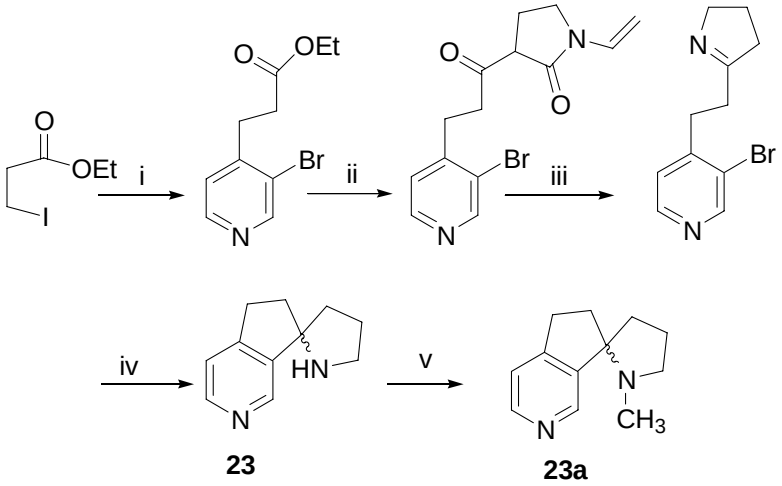
Scheme 8



Reagents: (i) Ac_2O; (ii) $PdCl_2(PPh_3)_2$, CuI, Et_3N, $HCCSiMe_3$; (iii) TBAF; (iv) $PdCl_2(PPh_3)_2$, CuI, Et_3N; (v) H_2, Pd/C, quinoline; (vi) $NaHCO_3$; (vii) $(Tf)_2O$, Et_3N; (viii) $Pd(OAc)_2$, (*R*)-BINAP, Et_3N; (ix) H_2, Pd/C; (x) KOH, $H_2NNH_2 \cdot H_2O$.

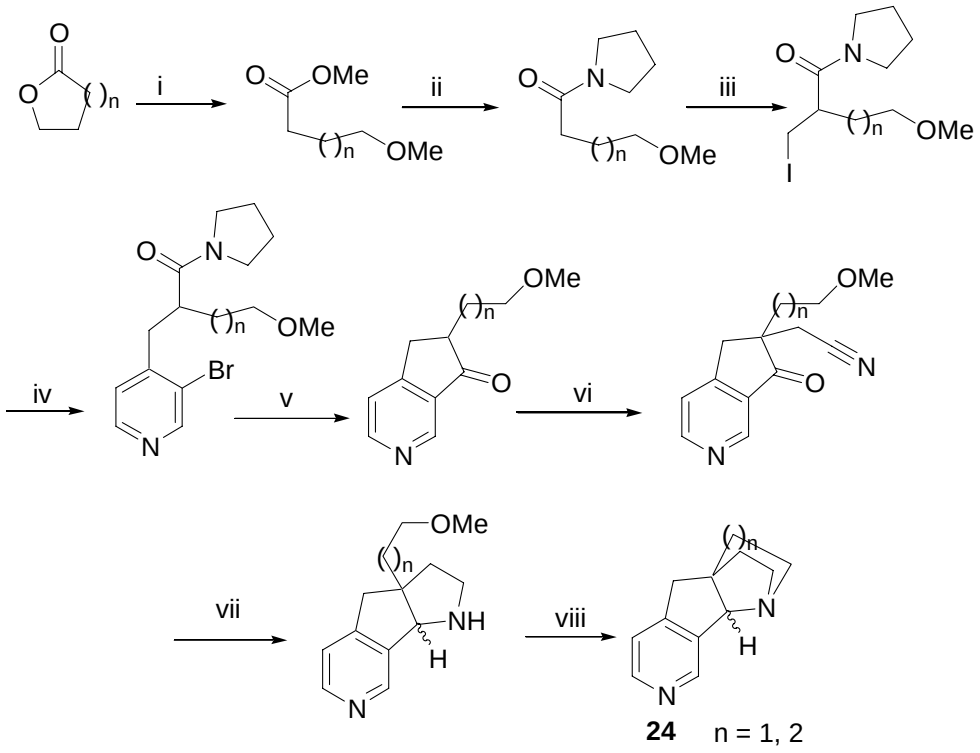
significant enantioselectivity over its antipode. This observation supports the hypothesis that conformational restraint can lead to high affinity ligands, which are stereochemically discriminated by nAChR and may feature optimum locations of the active sites of the pharmacophore. Very recently Yang et al.[40] synthesized conformationally constrained nicotines **17**, **10** and **18** via intramolecular azomethine ylide-alkene [3+2]-cycloaddition reaction which is shown in Schemes 11& 12.

Scheme 9



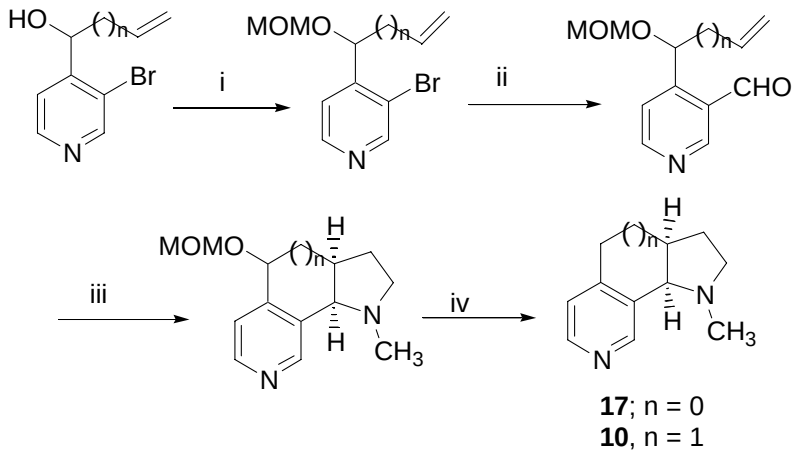
Reagents: (i) (a) Zn, LiCl, Cu; (b) 3-bromopyridine, ClCOOEt; (c) sulfur; (ii) *N*-vinylpyrrolidone, NaH; (iii) (a) 6 N HCl; (b) Na_2CO_3; (iv) *n*-BuLi; (v) HCHO, $NaBH_3CN$.

Scheme 10



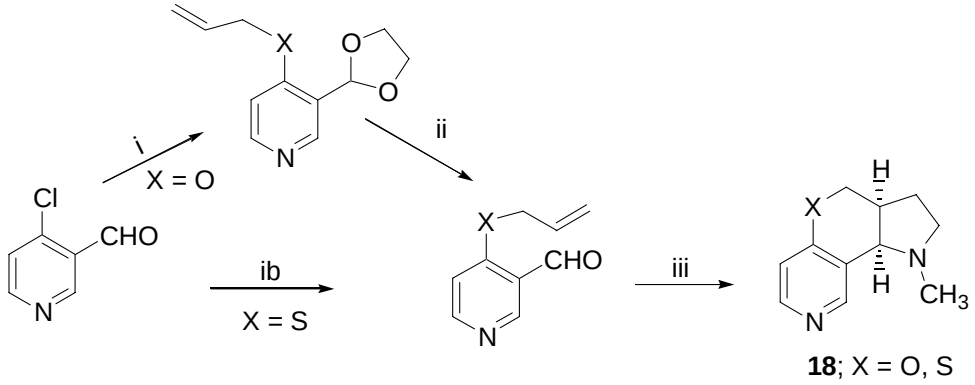
Reagents: (i) $HC(OMe)_3$, H_2SO_4 (cat.); (ii) pyrrolidine, NH_4Cl (cat.); (iii) (a) LDA, $BrCH_2Cl$; (b) NaI; (iv) (a) Zn, LiCl, Cu, (b) 3-bromopyridine, ClCOOEt; (c) sulfur; (v) *n*-BuLi; (vi) LDA, ICH_2CN; (vii) Raney-cobalt; (viii) (a) 62% HBr; (b) Na_2CO_3, H_2O.

Scheme 11



Reagents: (i) NaH, MOMCl; (ii) n-BuLi, DMF; (iii) sarcosine; (iv) (a) HCl, (b) Zn, HCO_2H.

Scheme 12



Reagents: (i) (a) $(CH_2OH)_2$, TsOH; (b) CH_2=CH-CH_2-XH (X = O, S), OH^-; (ii) $H_2C_2O_4$; (iii) sarcosine .

1.3. Pharmacophoric Models

In search of an understanding of the binding mode used by nicotinic ligands when interacting with nAChRs, different pharmacophoric elements have been proposed since 1970 as shown in Figure 5.[41, 17, 8]

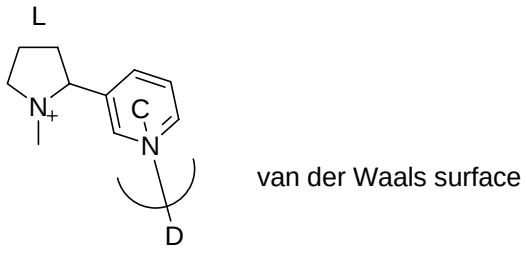


Figure 5. Proposed pharmacophoric elements in (*S*)-nicotine

Here (**N^+**) is a protonated nitrogen atom, (**N**) an electronegative atom capable of accepting a hydrogen bond, (**L**) a lipophilic site, (**C**) the centroid of a heteroaromatic ring

or a carbonyl carbon, and (**D**) a dummy atom representing a hydrogen bond donor atom in the receptor.

In 1970, Beers and Reich[42] proposed a pharmacophore from physical models of semirigid agonists and antagonists which was based on the distance between the pharamacophoric elements, i.e., a protonated nitrogen atom (**N^+**) and an electronegative atom capable of accepting a hydrogen bond, typically nitrogen or carbonyl oxygen (**N**). The distance between the centre of charge (**N^+**) and the centre of the van der Waals surface of the pyridine nitrogen was 5.9 Å (the Beers-Reich distance).[42] It has later been suggested that the angle between the line stretching from the charge centre (**N^+**) to the van der Waals surface, and the line from the hydrogen bond acceptor (**N**) to (**D**) is about 120°.[43] In fact, X-ray analysis of the strychnine crystal structure shows that the distance between the charged nitrogen to the van der Waals surface of the ether oxygen is 5.9 Å.[42] Furthermore, the distance between the homologous functional groups in nicotine, trimethaphan, cytisine and acetylcholine (Figure 6) agrees with the proposed model. However, this pharmacophore was inadequate to explain some cases. For example, the ferruginines in the *s-cis* conformation fit the Beers-Reich distance, but not the angle. Conversely, in the *s-trans* conformations, these agonists fit the angle fairly well but not the distance.[43] Additionally, two theoretical objections were raised as detailed below.

a) Although Beers and Reich emphasize the charge centre (usually a quaternary nitrogen) as a focus of coulombic attraction, *ab initio* molecular orbital calculations show that the positive charge is dispersed among the attached methyl groups[44, 45]; it is not centred on the nitrogen atom.

b) Beers and Reich assumed that the hydrogen bond forms along the line defined by the carbonyl bond. It may be guessed, however, that the hydrogen bond should be directed towards an orbital containing an unshared pair of electrons (i.e., at ± 60° from this line and the plane of carbonyl carbon and its substituents for the sp^2-hybridized orbitals of a carbonyl oxygen). Evidence in support of this has been reported. [46, 47]

In 1986 Sheridan and co-workers refined the above model on the basis of the structures of the nicotinic agonists (*S*)-nicotine, (-)-cytisine, (-)-ferruginine methiodide, and (-)-muscarone[48] (Figure 6). The essential modification in this pharmacophore was the

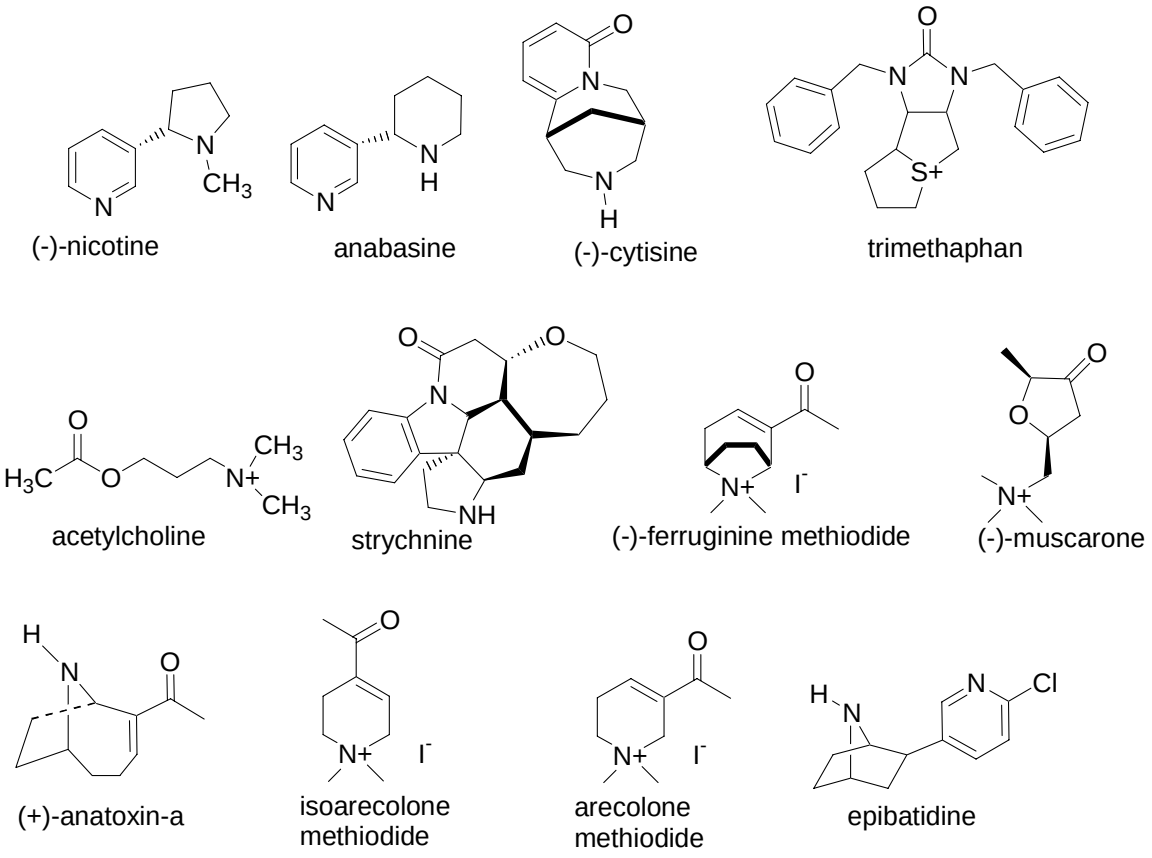


Figure 6

introduction of a point (**C**) or an atom, which defines a line along which the hydrogen bond may form. The optimal distances between the three points in the pharmacophore triangle were estimated to (**N^+-N**) 4.8 ± 0.3 Å; (**N^+-C**) 4.0 ± 0.3 Å; (**N-C**) 1.2 Å.[48] Comparing their results with those obtained by Beers and Reich, Sheridan and co-workers found that their pharmacophore also suggested the Beers-Reich distance to be 5.9 Å.

The Sheridan pharmacophore model based on four ligands did not implicitly consider functional or binding data. At the time the model was proposed, there was a paucity of nicotinic ligands and little understanding of multiple types of nACh receptors.

A later model[49] was derived by Manallack, Gallagher and Livingstone from (+)-anatoxin-a, isoarecolone methiodide, arecolone methiodide, (-)-ferruginine methiodide, (*S*)-nicotine, and (*R*)-epibatidine, using (-)-cytisine as a template for alignment. The involved pharmacophoric elements were

- the protonated nitrogen atom (**N^+**)
- the carbonyl carbon or pyridine ring centroid (**C**)
- a dummy atom (**D**) representing a hydrogen bond donor in the receptor placed 3Å away from the hydrogen bond acceptor, and
- a lipophilic region (**L**).

The lipophilic region was located close to the 3′, 4′ carbon atoms of the pyrrolidine ring in (*S*)-nicotine. The pharmacophoric elements were related by the following distances: (**N^+-C**) 3.94 Å, (**C-D**) 4.14 Å, (**N^+-D**) 6.48 Å, (**N^+-L**) 2.50 Å, (**C-L**) 4.07 Å, and (**D-L**) 6.70 Å. Compared to the original suggestion by Beers and Reich, the authors found a Beers-Reich distance of 5.4 Å and a **N^+-C-D** angle of 107°.[49]

In addition, recently a novel pharmacophore model was suggested by Tønder et al. [41, 50-52] based on the compounds shown in Figure 7. They reported that neither the inter nitrogen distance (**N^+-N**) nor the distance between the cationic centre and the hydrogen bond donor in the receptor (**N^+-b**) had any correlation with the affinity of the compounds (Figure 8).[52] In contrast to this, the distances between the site points **a**, **b**, and **c** in

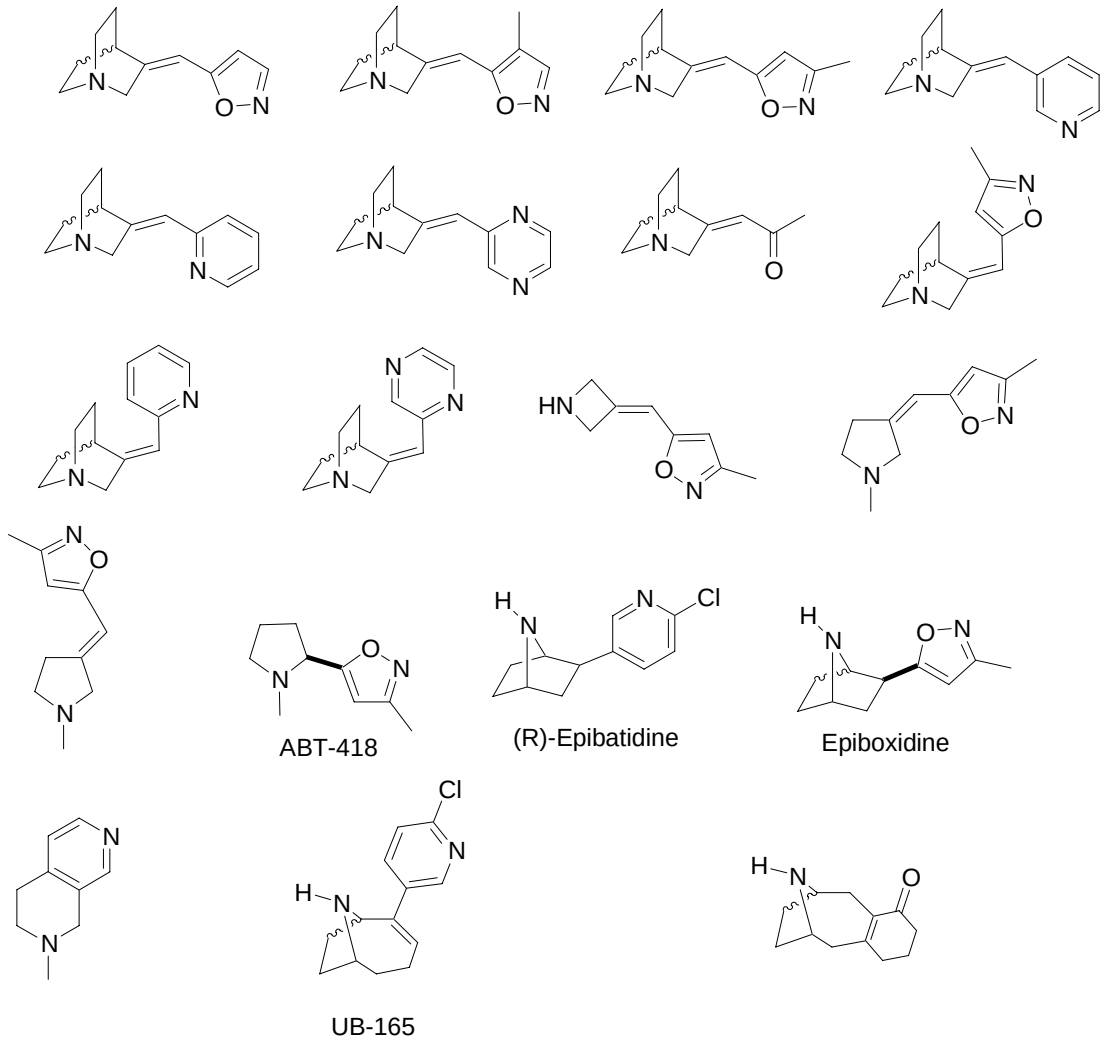


Figure 7*

* Structures with wavy lines mean that both the antipodes were considered in the computaional study.

addition to the angle between the interatomic distance vectors **a**-**b** and **a**-**c** were closely correlated to affinity. Thus, in order for a compound to possess high affinity for the nAChRs, the pharmacophoric parameters were required to be: (**a**-**b**) 7.3 – 8.0 Å; (**a**-**c**) 6.5 - 7.4 Å; (Δ**bac**) 30.4 - 35.8°.[52]

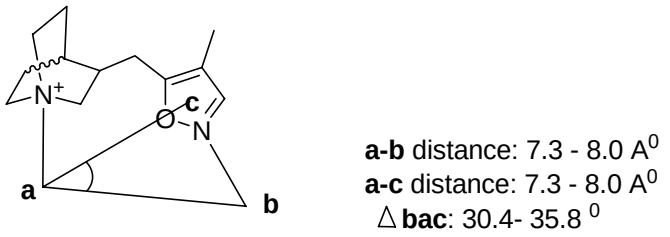


Figure 8: The definition of a novel nicotinic pharmacophore model.[52]

a is the site point corresponding to a protonated nitrogen atom, **b** is the site point corresponding to the electronegative atom capable of forming a hydrogen bond, **c** is the centre of a heteroaromatic ring or a C=O bond. Δ**bac** is the angle measured between interatomic distance vectors **a**-**b** and **a**-**c**. The site points **a** and **b** are placed 2.9 Å from the corresponding atoms in the direction of the lone pair.

Later Sharples et al.[18] applied this model to explain the pharmacological properties of a series of hybrid molecules based on anatoxin-a and epibatidine i.e. UB-165 analogues (Figure 9). The order of interaction potencies of these ligands towards nAChR α4β2* subtype are as follows: **26** > **27** > **30** = **31** > **32** >> **28**>> **29**. For deschloro UB-165 (**27**) the (a-b) distance (cf. Figure 8) and bac angle (Δbac) associated with Tønder pharmacophore[52] for the α4β2* type nAChR are 7.35 Å and 35.4º respectively, which match with proposed pharmacophore at global mimimum energy conformation.

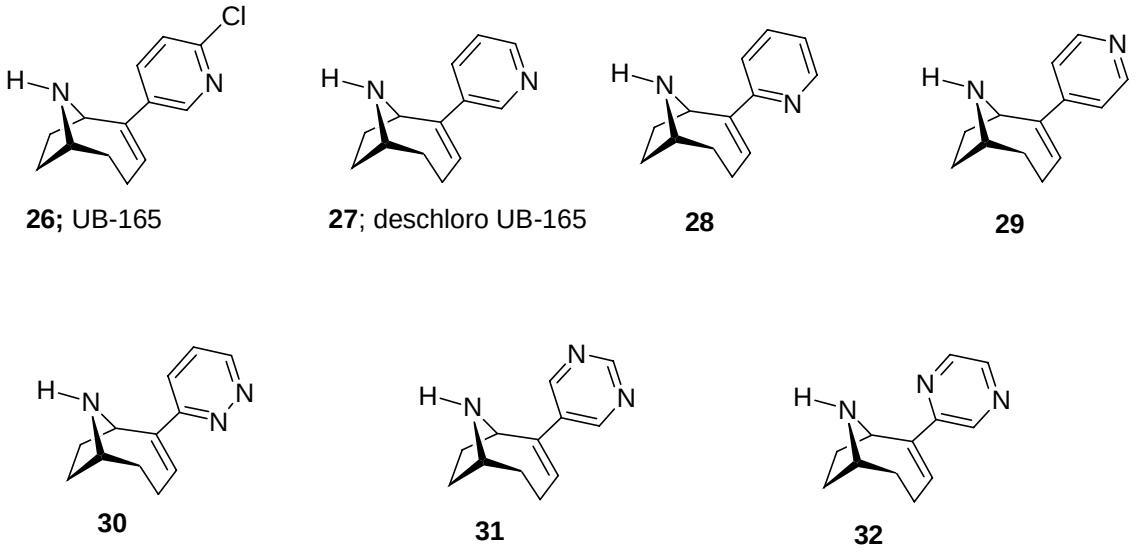
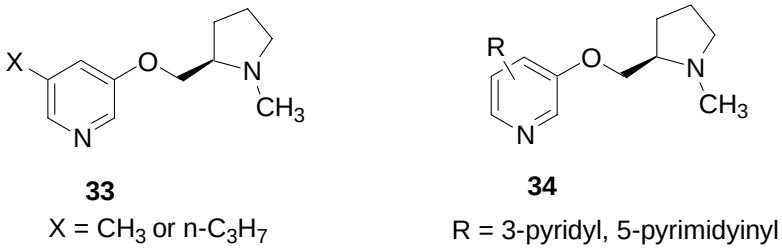


Figure 9

The (a-b) distances determined for **28**, range from 3.2 to 8.7 Å with the Δbac values of 25.6-35.8º. Obviously these values agree with the proposed model. In spite of this agreement this ligand **28** shows markedly reduced affinity for the α4β2* nAChRs. On the other hand the respective values for **29** are 10.1 Å and 25.4 º and these do not match with the model. This clearly explains the diminished binding affinity of **29** for α4β2* nAChR relative to **27** and **28**. Sharples et al.[18] also reported that like **27** the ligands **30**-**31** also conform to the basic pharmacophoric elements for the α4β2* nAChR because a 3′-pyridyl moiety is present in each of these ligands. Surprisingly, they possess nicotinic potencies for the α4β2* nAChR markedly different from that of **27**. Thus, Tønder pharmacophore is inadequate to explain the pharmacological activity of such type of ligands and these data according to them provide opportunity to refine the pharmacophore for α4β2* nAChR as well as develop pharmacophore models appropriate to other nicotinic receptor subtypes.[18] More recently, after the development of 3D-QSAR

analysis, researchers have drawn their attention to the three dimensional properties of ligands such as *steric and electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor properties*. Using this approach several quantitative models have been derived using sets of homologous molecules[53-57]or structurally diverse nicotinic ligands.[49, 52, 58, 59]

While the above mentioned models are helpful to rationalize the mode of interaction of ligands with the nAChR, some general remarks[9] can be made regarding their use in drug design. For example, molecules are included for which the affinity, but not their functional (agonistic or antagonistic) properties have been reported in the literature. It has been shown how small changes in the chemical structure may shift activity from agonist to antagonist: for instance, compound **33** (X = Me) (Figure 10) stimulates cation efflux in K177 cells while **33** (X = n-Pr), which differs only for two carbon units, blocks it;[60] compound **34** (R = 3-pyridyl) has antagonistic properties on IMR 32 cells expressing α3βx receptor, while **34** (R = 5-pyrimidinyl) is a partial agonist in the same preparation.[61] Thus, it is possible that at least some of the models were



33
X = CH_3 or n-C_3H_7

34
R = 3-pyridyl, 5-pyrimidyinyl

Figure 10

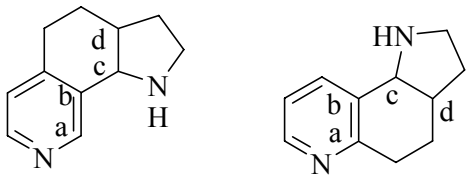
derived from compounds with different functional properties. However, the mixing of agonists and antagonists may be misleading, since agonists bind the desensitized state

with high affinity, while competitive antagonists prefer the closed state. Since these are two different conformational states of the receptor, also the geometry of the binding site may be different. Additionally, the models have been built using binding affinities determined usually on rat brain. Although it is generally accepted that most of the nAChRs in this tissue (90%) belongs to the α4β2 type,[62] many nAChR subunits are present that can coassemble to form multiple subtypes, and it has been shown that subunit composition can affect the affinity of ligands.[63] To date, although novel agents have been identified that fit some of the models, the models themselves have not been used to design novel agents.[17] According to Romanelli and Gualtieri "*the useful hints about how to design selective compounds can hardly be drawn from such models. Therefore, more binding and functional data on different nAChR subtypes are necessary to understand the structural requirements for selectivity, which, at present, is probably the most important goal in the field of nicotinic ligands"*.[9] It may also be appropriate to quote from a recent overview of α4β2 nAChR receptor pharmacophore models by Glennon and Dukat "…… ….even with 50 years of history nicotinic pharmacophore models still require extensive work."[17]

2. Previous work from this laboratory

A major emphasis of our research work in this laboratory has been to develop novel conformationally restricted analogues of nicotine which will exhibit high affinity and subtype selectivity for nAChRs without inducing typical nicotine-like side effects

(gastrointestinal and cardiovascular). In order to accomplish this goal, Sarkar et al. settled on the reported conformationally restricted analogues of nicotine, e.g. **35** and **36** (Fig. 11)



35 **36**

Figure 11

because they provide a reasonable mimic of the two trans conformers of nicotine that is supported by crystal structure data.[36] It may be mentioned here that for the monoprotonated species of nicotine in aqueous solution, there are four major conformations present, of which the two approximately isoenergetic *trans* rotamers are preferred over their *cis* counterparts by > 10:1 (Fig. 12).[64] Like others[36] we envisioned that the ability to "freeze out" the conformational dynamics of nicotine at various torsion angles (*abcd*) maintaining skew orientation of pyridine and pyrrolydine rings as in **35/36** might help to identify conformational factors which appear to be critical for interaction

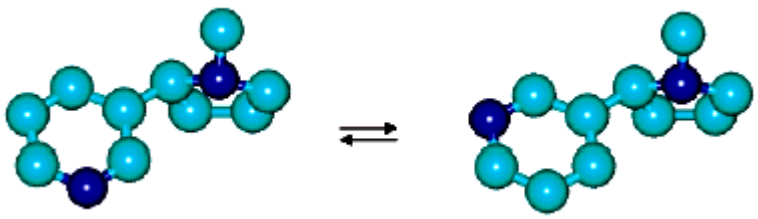


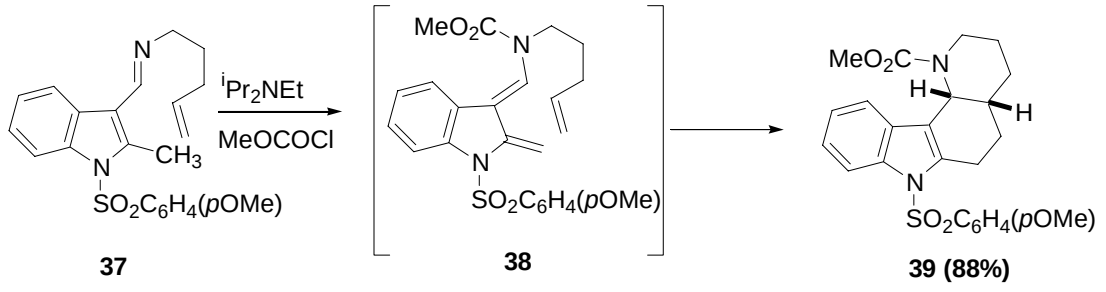
Figure 12

with various nAChR subtypes. *The binding units or additional substituents which may be used to restrict the conformational flexibility of nicotine may themselves interact with the portion of binding site, either favorably or unfavorably, and in turn impart some selectivity for one subtype or another.*

During the past two decades (1983-2003), only one synthetic route* has been developed for the synthesis of the ring systems, e.g. **35** and **36** as shown in Scheme 4. However, this route does not appear to be viable for the synthesis of a large diversity of bridged nicotines and anabasines required to probe the conformation of (*S*)-nicotine which induces ion channel opening. Therefore, development of an alternative route which would be straightforward, high-yielding, and flexible is desirable. Our group has addressed this issue and this is discussed here-in-after.

In 1981 Gallagher and Magnus[65] reported an elegant strategy for the in situ generation and trapping of indole-*o*-quinodimethanes, e.g. **38** as shown in Scheme 13. This work formed the basis for the synthesis of a large number of complex indole alkaloids by this group.[66] Subsequently, this strategy was followed by van Leusen and co-workers for the generation and trapping of pyrrole-2,3-quinodimethanes.[67]

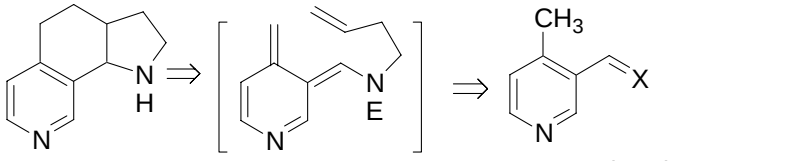
Scheme 13



* An alternative synthetic approach to the ring system **35** has been described (see Scheme 11) by Yang et al.[40]; however, this report appeared after completion of the work described in this chapter.

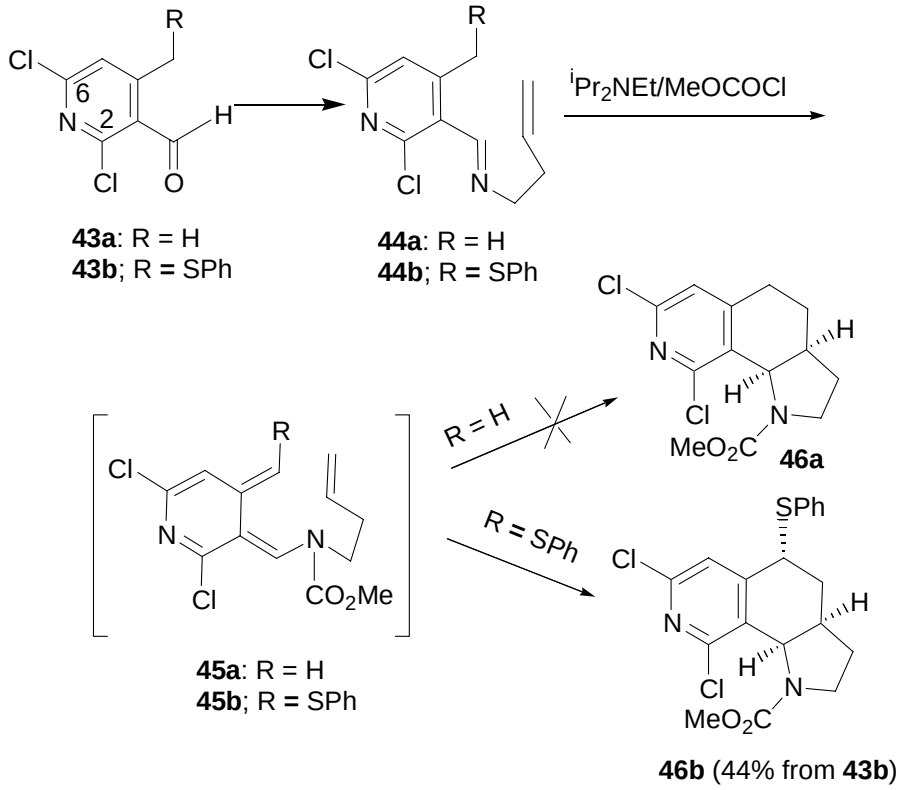
Based on the pioneering work of Gallagher and Magnus,[65] Sarkar *et al*. initiated work on a strategically different approach to compounds of the type **35** via generation of pyridine *o*-quinodimethane **42** through a formal imine tautomerisation of **41** and its intramolecular trapping; imine **41** can be made from its corresponding aldehyde **40** (Scheme 14).[68]

Scheme 14



To investigate the feasibility of this approach, the imine **44a** was synthesized from the dichloro-substituted aldehyde **43a** (Scheme 15). The choice of chloro substituents flanking the pyridine nitrogen was crucial for this study: the C-2 chloro group was selected for enhanced *cis*-stereoselectivity at the ring juncture in the Diels-Alder step, while the C-6 chloro group was chosen for stronger binding affinity of constrained nicotines and anabasines toward nAChRs. Unfortunately, treatment of **44a** with methyl chloroformate in the presence of Hünig's base and refluxing the mixture in xylene for an extended period[65] did not give any traces of **46a**. This failure was thought to be due to (i) the low acidity of methyl hydrogen which does not lend itself to rapid abstraction, (ii) recalcitrance of the pyridine nucleus to give up its aromaticity, or (iii) in situ generated *o*-quinodimethane intermediate being not sufficiently reactive to allow a Diels-Alder reaction to occur. In order to overcome these problems it was considered

Scheme 15



important to replace one of the hydrogens on the methyl group in the imine by a substituent which would not only make the methyl hydrogens more acidic (cf. **41**) but also stabilize the *o*-quinodimethane intermediates (cf. **42**). A phenylsulfanyl group appeared to fulfil these criteria; also it lends itself to easy reductive removal. In the event, imine **44b** was made from the readily available aldehyde **43b**. The formal imine tautomerisation reaction using methyl chloroformate in the presence of diisopropylethylamine this time gave the desired constrained nicotine **46b** as a white crystalline solid in 44% yield. This methodology was found to work satisfactorily for the synthesis of a large number of conformationally restricted nicotines as well as anabasines.[68]

Pharmacological characterization of some of the synthesized conformationally constrained analogues at activating $\alpha_3\beta_4$ nAChRs was also investigated by Sarkar et al.,[68, 69] and constrained nicotine analogue **47** as well as constrained anabasine analogues **48** and **49** were found to exhibit moderately potent nicotinic agonist activity (Figure 13). *It can be mentioned that previous pharmacophore models emphasize on π-cation interaction for subtype selectivity. However, the pyrrolidinic nitrogen in **47**, **48** and **49**, cannot undergo protonation under physiological conditions as the same is bound to a carbomethoxy group. Thus, molecules such as **47**, **48** and **49** do not relate to existing pharmacophore models. Therefore, a refined nicotinic pharmacophore model needs to be developed to accommodate such molecules.*

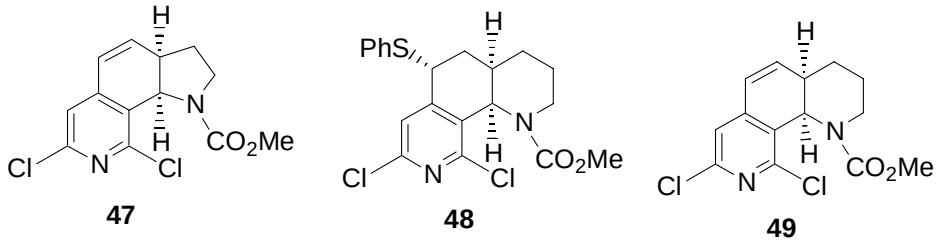


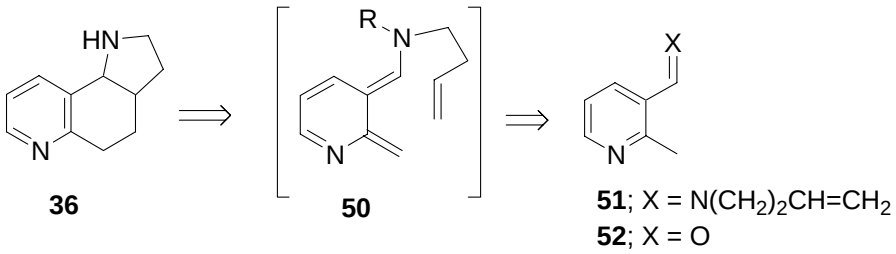
Figure 13

3. Present work

The foregoing encouraging results on the synthesis and pharmacological evaluation of constrained nicotines and anabasines prompted us to undertake a similar investigation with the other nicotinic mimic, e.g. **36**. In line with the previous work, our strategy for the new analogues is depicted in Scheme 16. It was also deemed important to introduce chloro- and sulfanylmethyl-substituents at the appropriate positions on the

pyridine ring and study their roles towards the efficiency and stereoselectivity during the ring-forming step.

Scheme 16



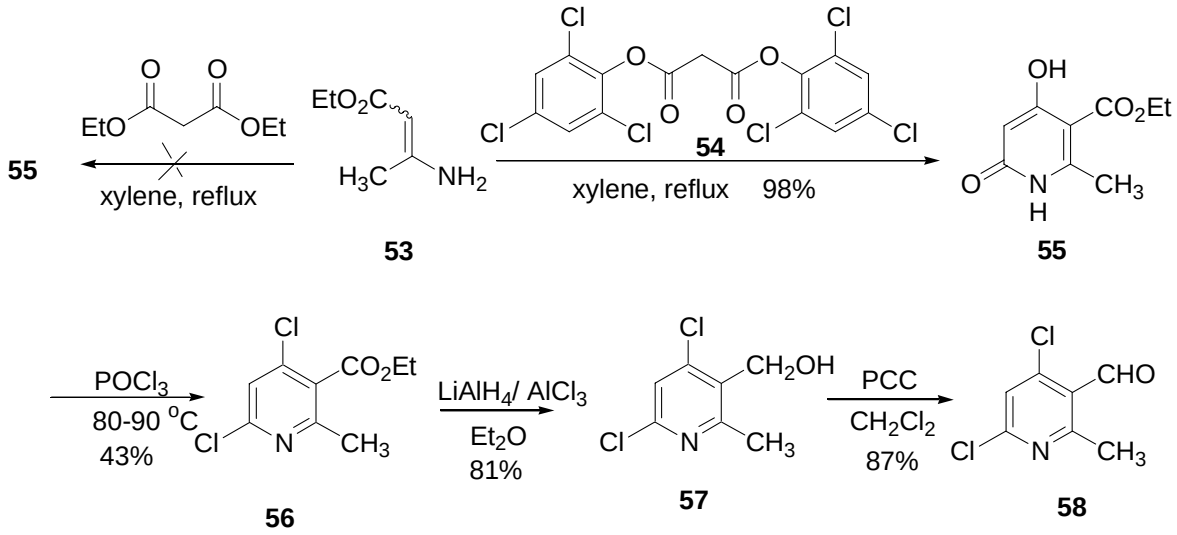
36 **50**

51; X = $N(CH_2)_2CH=CH_2$
52; X = O

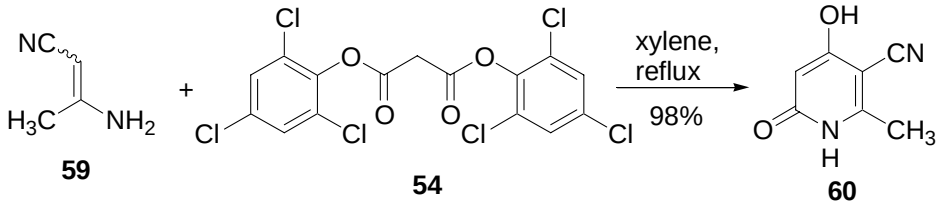
4. Results and Discussion

Our present investigation began with the synthesis of pyridine carboxaldehyde **58** (Scheme 17). Incidentally, this compound has not been reported in the literature till date. In this regard we have developed a new route for the preparation of ethyl 4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (**55**) (Scheme 17). We initially attempted the condensation of ethyl 3-aminocrotonate (**53**) with diethyl malonate. However, this reaction failed. We then found from the literature that Kappe and Soliman[70] used bis-2,4,6-trichlorophenylmalonate (**54**)[71] instead of diethyl malonate for a similar condensation reaction (Scheme 18). When **53** was treated with bis-2,4,6-trichlorophenylmalonate (**54**) in refluxing xylene **55** was produced as a grey solid in high yield (98%) (mp 225-228 °C)[72a]. Presumably this condensation worked due to better leaving group ability of the trichlorophenoxy group of **54**. Compound **55** is reported in the literature, but methodologies followed for its preparation suffer either from poor

Scheme 17

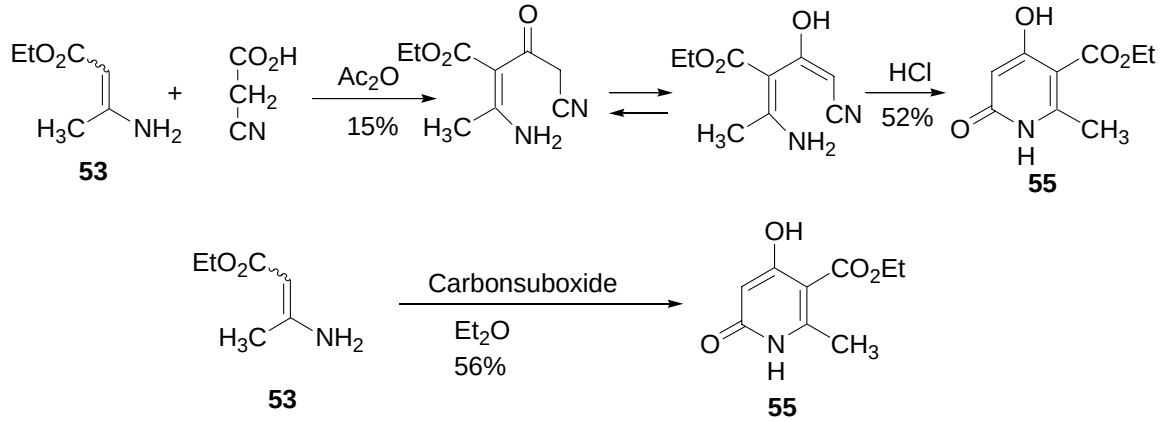


Scheme 18



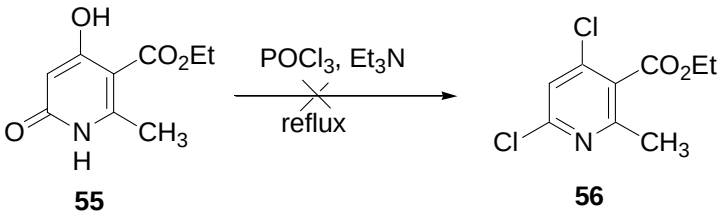
yield (8%) when **53** is exposed to cyanoacetic acid in acetic anhydride as solvent followed by treatment with acid[72a] or inconvenience due to lack of availability of reagents (e.g. carbonsuboxide)[72b, 73] (Scheme 19). Exposure of **55** to $POCl_3$ at 80-90 °C

Scheme 19



gave ethyl 4,6-dichloro-2-methyl-3-nicotinate (**56**) in 43 % yield (Scheme 17). Surprisingly, Stadlbauer *et al*. did not succeed to synthesize **56** from similar treatment of **55** with $POCl_3$ in presence of triethylamine under refluxing condition (Scheme 20).[73] Presence of molecular ion peak at m/z 234 ($[M+H]^+$, $C_9H_{10}Cl_2NO_2$) in mass spectrometry and a strong absorption band at 1730 cm^{-1} due to the ester group in IR suggested the

Scheme 20

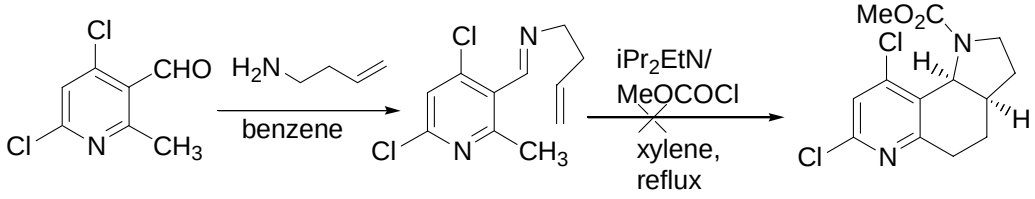


formation of the dichloro compound **56**. In ^1H NMR the presence of two singlets at δ 7.26 and 2.54 for pyridine and methyl protons, a quartet at 4.42 due to the $CO_2CH_2CH_3$ and a triplet at 1.40 for $CO_2CH_2CH_3$ supports the structure. Additionally, the presence of 9 lines in ^{13}C NMR confirms the structure of **56**. Reduction of the ester group in **56** to alcohol **57** was achieved by lithium aluminum hydride in presence of $AlCl_3$ in ether.[74] In the absence $AlCl_3$ reductive elimination of chlorine might have given a poorer yield of the required product. Alcohol **57** was oxidized by PCC in CH_2Cl_2 to give the aldehyde **58** as a pale yellow solid (mp 42 – 44 °C) in 87% yield. Formation of the aldehyde **58** is evident from spectral data. Presence of molecular ion peak at m/z 190 ($[M+H]^+$, $C_7H_6Cl_2NO$) in mass spectrometry and a strong absorption band at 1700 cm^{-1} due to the aldehyde carbonyl in IR reveals the formation of aldehyde **58**. In ^1H NMR the presence of three singlets at δ 10.56 for C*H*O, 7.33 for pyridine proton and at 2.75 for CH_3 agreed

with the structure. In ^{13}C NMR presence of a methine signal at δ 189.4 due to *C*HO, methyl carbon signal at 24.1 along with other 5 lines confirms the structure of **58**.

Initial studies were made with imine **61**, generated from the reaction of **58** with 3-butenylamine, and this was heated to reflux in xylene in presence of Hünig's base and methyl chloroformate. Unfortunately, no traces of required Diels-Alder adduct **62** was obtained (Scheme 21). This was of course not an unexpected result based on previous work of Dr. S. Basak from this laboratory.[68] This failure led us to synthesize the

Scheme 21

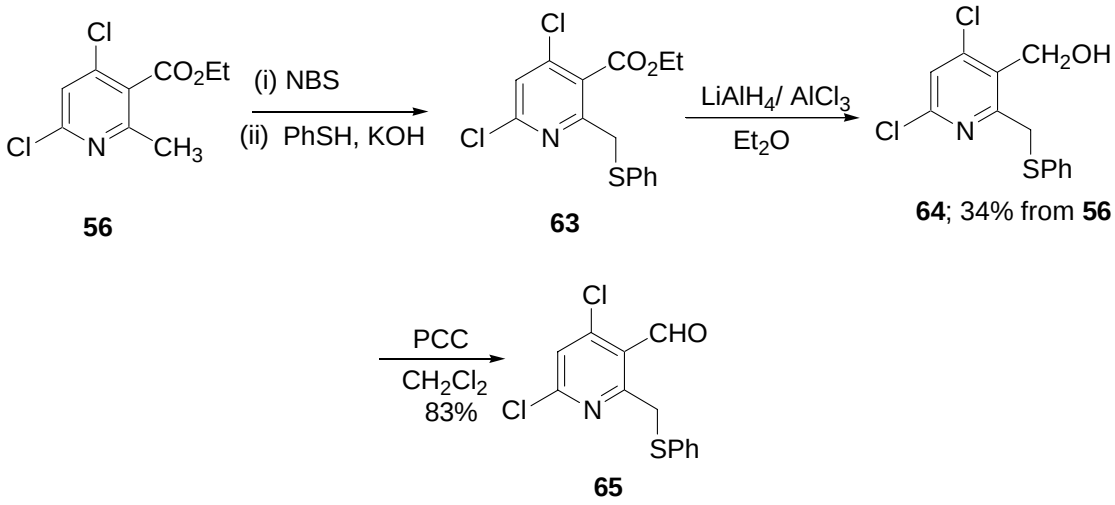


58 **61** **62**

phenylsulfanyl substituted pyridinecarboxaldehyde **65** as follows. Benzylic bromination[75] of **56** (Scheme 22) followed by substitution of the bromide by phenylsulfanyl group and reduction ($LiAlH_4$-$AlCl_3$) gave **64**. It may be mentioned here that the ester **63** was not obtained in a pure state. Indeed spectral data revealed that it was contaminated with **56**. Fortunately, the pure alcohol **64** was isolated from column chromatography after reduction of **63** (+**56**) with lithium aluminum hydride in presence of $AlCl_3$ in an overall yield of 34% from **56**. Presence of molecular ion peak at m/z 300 ($[M+H]^+$, $C_{13}H_{12}Cl_2NOS$) suggested the formation of alcohol **64**. In ^1H NMR the presence of multiples at δ 7.55-7.20 for SC_6H_5, singlets at 4.80 and 4.35 for two methylene protons agreed with the structure. Furthermore, presence of 11 lines in ^{13}C NMR confirmed the structural assignment. Oxidation of the alcohol **64** with PCC afforded **65** as a yellow oil. Presence of molecular

ion peak at m/z 298 ($[M+H]^+$, $C_{13}H_{10}Cl_2NOS$) in mass spectrum and absorption band at 1704 cm^{-1} due to carbonyl group reveals the formation of aldehyde. Presence of a characteristic singlet at δ 10.46 due to C*H*O in ^1H NMR and appearance of signal at 189.0 due to *C*HO in ^{13}C NMR confirms the formation of aldehyde **65**.

Scheme 22

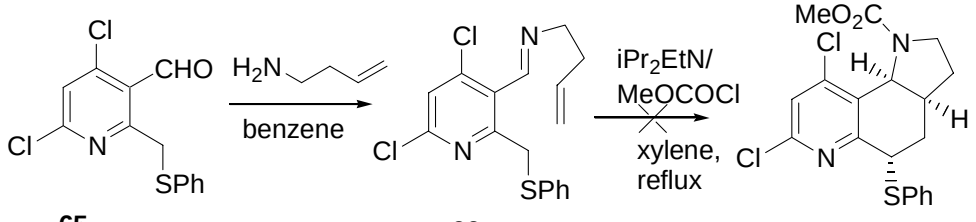


56 **63** **64**; 34% from **56**

65

Once again no Diels-Alder adduct, e.g. **67** was obtained when the imine **66** obtained from **65**, was refluxed with methyl chloroformate in presence of Hünig's base in xylene for a prolonged period (Scheme 23).

Scheme 23



65 **66** **67**

This result was most surprising considering the fact that a similarly substituted imine, e.g. **44b** underwent smooth formal tautomerisation followed by cycloaddition to

give the constrained nicotine **46b**. We wondered at this stage if acidity of the protons attached to the carbon carrying the phenylsulfanyl group in **66** was the issue. It was then decided to try the same reaction with 5-nitro substituted imines **68/ 69** (Figure 14). The substrate **69** was actually selected because we were apprehensive that synthesis of **68** from the corresponding aldehyde would pose problems due to the competitive displacement of the chloro group(s) by the amine. Indeed, such types of reactions are reported in the literature.[76] For example reaction of chloro substituted ester **70** with a primary amine results in displacement of chloro group to give **71** as the major product (Scheme 24). [76] We of course realized that removal of the chloro groups might hamper stereoselectivity and/or biological activity of our target molecules, but further studies were conducted on **69** due to our eagerness to succeed at the cycloaddition step. As we shall see later (vide infra) *stereochemistry indeed raised its ugly head*.

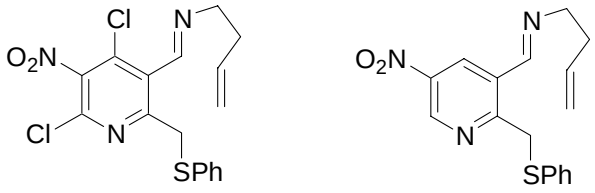
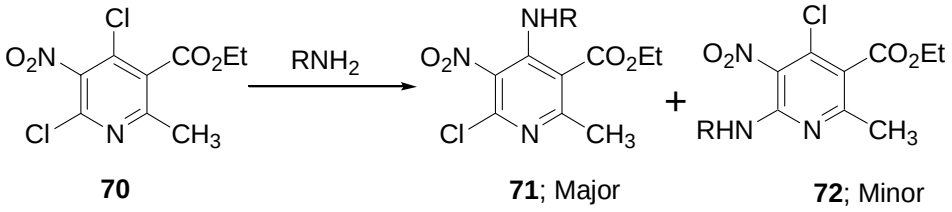


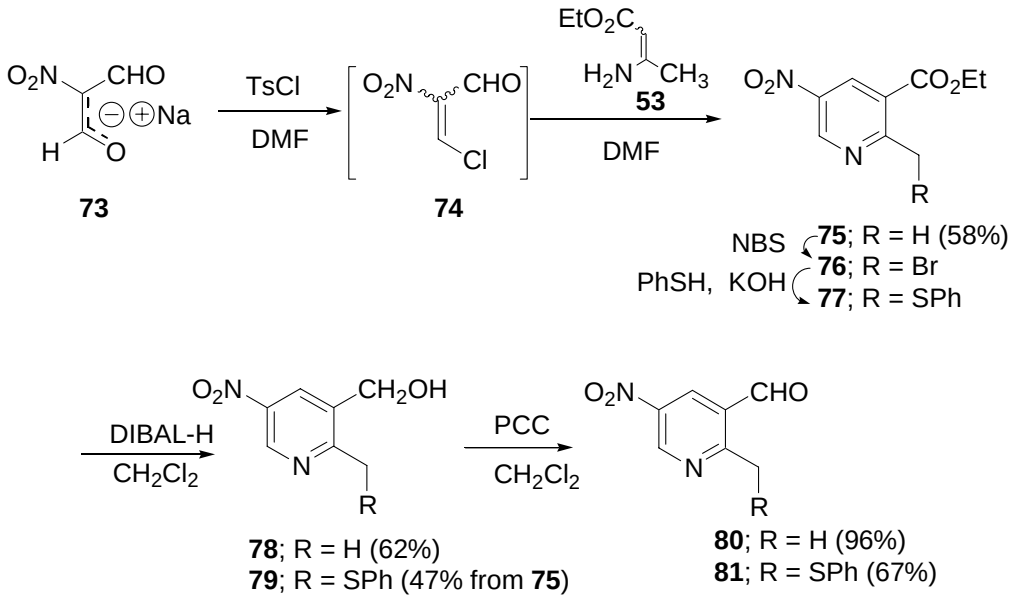
Figure 14

Scheme 24



For the synthesis of **81**, our studies began with the known ester **75**,[77] prepared from the reaction of 3-aminocrotonate (**53**) with the highly active Michael acceptor **74**, generated in situ from **73** [78] (Scheme 25). Reduction of **75** with DIBAL-H in dichloromethane gave the alcohol **78**. Presence of molecular ion peak at m/z 169 ($[M+H]^+$, $C_7H_9Cl_2N_2O_3$) reveals the formation of alcohol **78**. In ^1H NMR the presence of doublets at δ 9.23 and 8.58 for 2 pyridine protons, two singlets at 4.83 and 2.62 for CH_2OH and CH_3 protons supports the formation of alcohol. Presence of 7 lines in ^{13}C NMR confirms the structure. Oxidation of **78** with PCC at room temperature in dichloromethane gave the aldehyde **80** as a yellow crystalline solid (mp 64-65 °C). The phenylsulfanyl substituted aldehyde **81** was also made from **75** via the bromide, displacement of the latter with potassium thiophenolate and reduction followed by oxidation. Like in the case of **63** the thiosubstituted ester **77** was not obtained in a pure

Scheme 25

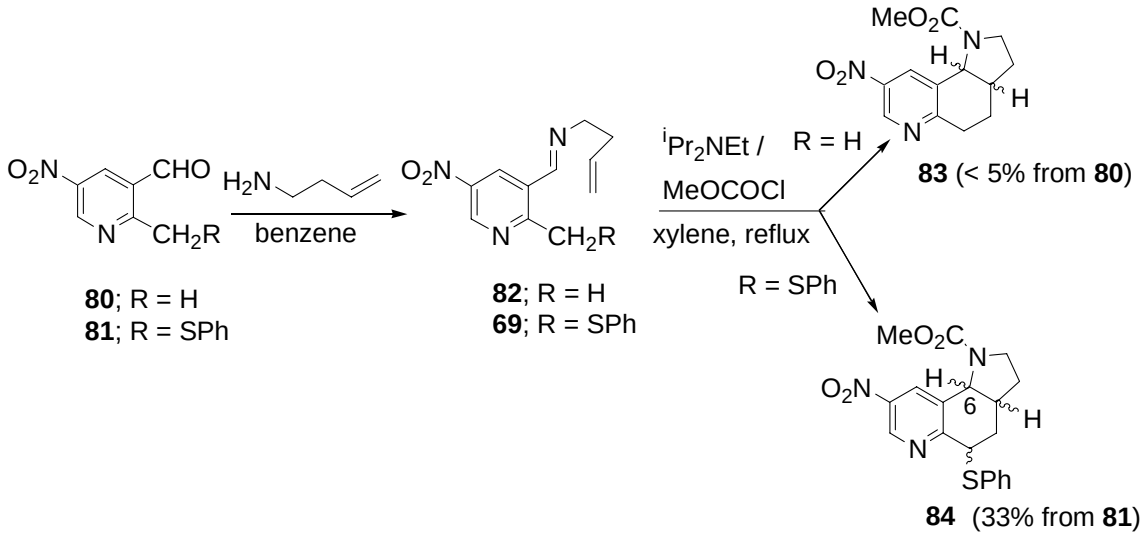


state. Rather it was found from the relative intensities of CH_2SPh and CH_3 groups in ^1H NMR to be contaminated with ~20% of **75**. At this stage it was hard to separate these two compounds by column chromatography and so the mixture was subjected to reduction. Thus, treatment of the above mixture with DIBAL-H in dichloromethane at -10 → -5 °C gave pure alcohol **79** in an overall yield of 47% from **75**. Formation of alcohol was evident from spectral data. Oxidation of **79** with PCC gave the aldehyde **81** in good yield. Presence of molecular ion peak at m/z 275 ($[M+H]^+$, $C_{13}H_{11}N_2O_3S$) and absorption band at 1704 cm^{-1} in IR due to carbonyl group reveals the formation of aldehyde **81**. In ^1H NMR the presence of two singlets at δ 10.16 for C*H*O and 4.66 for CH_2SPh, doublets at 9.41 and 8.86 for 2 pyridine protons and a multiplet at 7.40-7.24 for SC_6H_5 protons supports the formation of the aldehyde. Additionally, presence of a methine carbon signal at δ 187.4 due to *C*HO in ^{13}C NMR further confirmed the structure of **81**.

When **80** was treated with 3-butenylamine, with provision for removal of water by anhydrous Na_2SO_4 and molecular sieves (4 Å) imine **82** was formed (Scheme 26). Although imine **82** is quite unstable in air, it was possible to characterize it from ^1H NMR which shows signals at δ 8.54 (bs, C*H*=NHC), 5.90-5.73 (m, C*H* = CH_2) and 5.14-5.05 (m, CH=CH_2). When imine **82** was treated with methyl chloroformate in presence of Hünig's base under refluxing condition it gave only traces (≤ 5%) of the tricyclic product **83**. The structure of **83** was ascertained from ^1H NMR which shows a characteristic signal for -CO_2*Me* at δ 3.82 (s) along with disappearance of the vinylic protons of **82**. LCMS of **83** is also supportive of its structure which shows $[M+H]^+$ at *m/z* 278 ($C_{13}H_{16}N_2O_4$) as a base peak. In spite of this disappointing result this experiment proves that acidity of the methyl protons of **82** and possibly stability of the *in situ* generated *o*-

quinodimethane intermediate provide the driving force for the ultimate reaction. Gratifyingly, when **81** was treated with 3-butenylamine and the resultant imine **69** heated with methyl chloroformate in presence of Hünig's base, the constrained nicotine analogue **84** was formed as an oil in about 33% yield (Scheme 26). TLC indicated it to be a single compound. The structure of **84** was assigned on the basis of extensive NMR (^{1}H and ^{13}C NMR, 1D homonuclear decoupling experiments, COSY experiment) and HRMS data. ^{1}H NMR of **84** shows a characteristic doublet at δ 5.38 (1H, J = 8.2 Hz) for C_6-*H* proton

Scheme 26



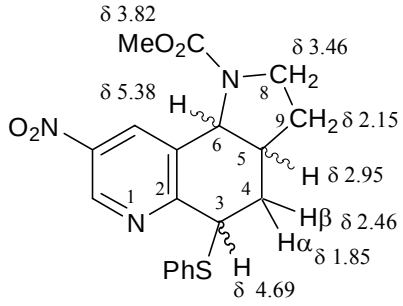
80; R = H
81; R = SPh

82; R = H
69; R = SPh

with the disappearance of signal for vinylic protons of **69**. The presence of the CO_2*Me* group is evident from the appearance of a sharp singlet at δ 3.82. ^{13}C-NMR of **84**, however, shows 16 lines instead of the expected 17. This discrepancy may be due to either overlapping of a pair of signals or disappearance of a weak signal in the noise region. The details of 1D homonuclear decoupling, COSY, mass spectra are discussed here-in- under.

1D Decoupling Experiments

Irradiation at δ 5.38 (C_6-*H*) changes spectral pattern only at δ 2.95. Also, irradiation at 2.95 results in collapse of the 2 line signals at 5.38 into a singlet and simplification of the spectral pattern at δ 2.15, 2.46, 1.85 which then should be due to C_5-*H*. Irradiation at δ 3.46 changes the spectral pattern only at δ 2.15, whereas irradiation at δ 2.15 changes the spectral pattern at δ 3.46 and δ 2.95. This indicates that the signals at δ 3.46 are most likely due to C_8-protons and signals at 2.15 is due to C_9- protons. Irradiation at δ 2.46 changes the spectral pattern at δ 1.85 and δ 2.95 (C_5-*H*) along with the simplification of the coupling pattern at δ 4.69. In addition, irradiation at δ 1.85 changes the spectral pattern at δ 2.95 (C_5-*H*), δ 2.47 and simplification of the coupling pattern at δ 4.69. This clearly indicates that signals at δ 2.46 and δ 1.85 are due to the two geminal protons attached with C_4 whereas signal at δ 4.69 is due to C_3-*H*.



2D COSY Experiment

The 2D COSY experiment shows the connectivity of the protons at δ 5.38 and δ 2.95, which proves that δ 5.38 and δ 2.95 are due to C_6-*H* and C_5-*H* respectively. Similarly, connectivity is also observed for the protons C_3-*H* (δ 4.69) with C_4-H_β (δ 2.46) and C_4-H_α (δ 1.85). In the same way, this experiment also established the following

connectivities for protons: δ 3.46 (C_8-H_2) and δ 2.15 (C_9-H_2); δ 2.95 (C_5-H) with δ 2.15 (C_9 -H_2), δ 1.85 (C_4-H_α), δ 2.46 (C_4-H_β), δ 5.38 (C_6-H); δ 2.46 (C_4- H_β), δ 2.95 (C_5-H), δ 4.69 (C_3-H) and δ 1.85 (C_4- H_α). Thus, from COSY as well as 1D decoupling experiments the position of protons in the aliphatic region are assigned and the following connectivities for protons from COSY sequence is evidently present.

C8-H/C9-H → C9-H/C5-H → C5-H/C4-H → C4-H/C3-H

↓

C5-H/C6-H

Therefore, 2D COSY experiment supports the structure **84**.

ESI MS and HRMS data

ESI MS of **84** shows signals at *m/z* 408 for $[M+Na]^+$ as base peak with the molecular ion peak at *m/z* 386 ($[M+H]^+$, 60%). Other fragmentation peaks at *m/z* 339 for $[M-NO_2]^+$ (5%), 276 for $[M-SPh]^+$ (22%) also support the composition of **84**.

In HRMS (ESI), the calculated *m/z* for $C_{19}H_{20}N_3O_4S$ is 386.1175 agreed with the observed value of 386.1161.

The stereochemistry of **84** was at first assigned from NOE difference experiments as follows.

NOE difference experiments

The relative stereochemistry at C_5, C_6 and C_3 was determined from NOE-difference experiment. Thus, irradiation at δ 5.38 (C_6-H) resulted in a significant enhancement of the signal at δ 2.95 (C_5-H, ~10%) whereas irradiation at δ 2.95 (C_5- H) enhances the signal at δ 5.38 (C_6-H, ~10%) and thereby establishes the *cis*

stereochemistry of the C_6-*H* and C_5-*H* junction protons. However, no NOE was observed at δ 4.69 for C_3-*H*, when C_5-*H* was irradiated. This establishes that the phenylsulfanyl group is *cis* to C_5-*H* and C_6-*H*. All these experiments suggest that the stereochemistry of **84** should be as given in Figure 15. Although the NOE difference experiments show that the BC ring is *cis* fused, the coupling constant (J_{ab}) is quite high (J_{ab} = 8.2 Hz). Based on literature reports (Figure 16) one would expect that the coupling constant in this case should be about 5-7 Hz for *cis* configuration and 10-12 Hz for *trans* configuration.

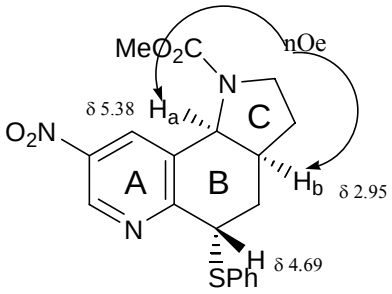


Figure 15

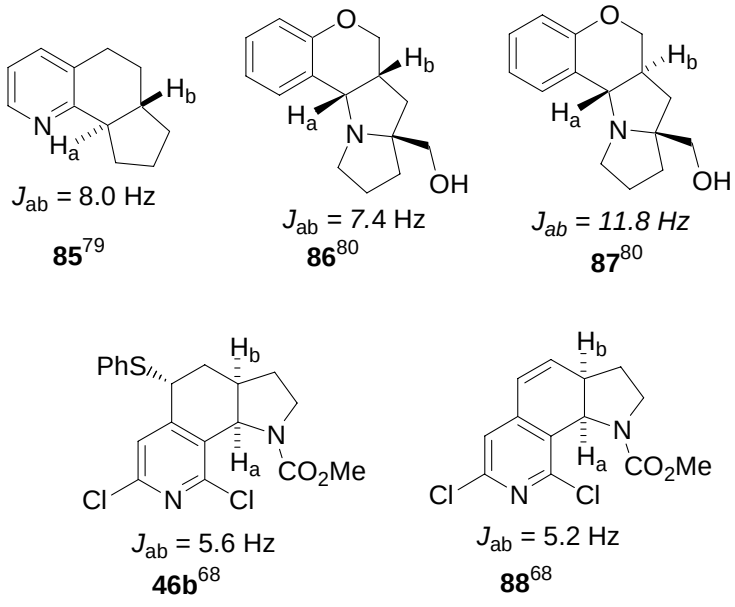
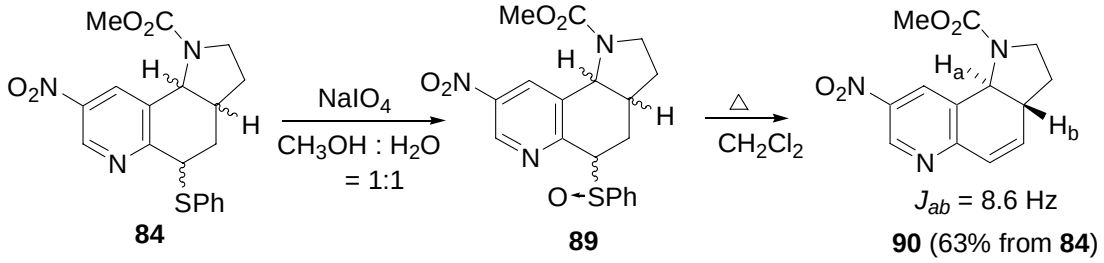


Figure 16

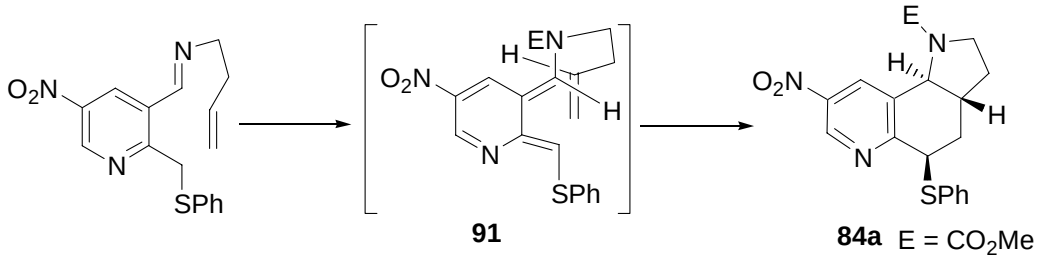
So, at this stage we were not absolutely sure about the stereochemistry of **84** and it needed further studies. Thus, exposure of **84** to $NaIO_4$ in MeOH:H_2O (1:1) gave the sulfoxide **89** and some amount of eliminated product **90** (Scheme 27). Refluxing **89** in dichloromethane gave **90** in acceptable yield as a yellow oil. Structure of **90** is fully supported from spectral data. Presence of molecular ion peak at m/z 276 ($[M+H]^+$, $C_{13}H_{14}N_3O_4$) in mass spectrum and a strong absorption band at 1696 cm^{-1} in IR due to CO_2Me group suggest the formation of product **86**. In ^1H NMR ($CDCl_3$) the disappearance of the signals for SPh group at δ 7.24-7.56 and appearance of characteristic

Scheme 27



signals at 6.73 (d, 1H, J = 10 Hz) and 6.61-6.42 (m, 1H) for the vinylic protons supports the formation of **90**. Additionally, presence of 13 lines in ^{13}C NMR confirms the formation of product **90**. Here again we found that the coupling constant J_{ab} is 8.6 Hz (Scheme 27) and this is not agreeable with the *cis* stereochemistry at the ring juncture. So, it may be concluded that the conformationally restricted nicotine, that is **90** is *trans* fused. Further analysis based on the original work of Gallagher and Magnus[64] shows that the most favourable transition state of the pyridine *o*-quinodimethane intermediate from **69** should be **91** (Scheme 28) and, therefore, the stereochemistry of the cycloadduct should be **84a**.

Scheme 28



5. Conclusion

In conclusion, a synthesis of constrained nicotine analogues **84a** and **90** has been achieved. Furthermore, the importance of electron withdrawing group on the pyridine ring and of the phenylsulfanyl group in the pyridine sidearm has been demonstrated as in the earlier work[68] reported from our laboratory. Although the structure of **84a** is evident from extensive NMR, HRMS data and transition state analysis, further investigation may be needed to confirm its stereochemistry via preparation of a solid derivative and X-ray crystal structure determination of the latter.

6. Experimental

2,4,6-Trichlorophenol [81]

To a vigorously stirred solution of phenol (9.6 g, 0.1 mol) in conc. HCl (150 ml) was added 30% H_2O_2 (40 ml) dropwise at 0 °C over a period of 30 min. Then the reaction mixture was heated at 60 °C for 4h during which orange solid was formed. After filtration, washing and drying 19.8 g (98%) of the *title compound* was obtained.

Mp 68 C °C (lit.[81] 71 °C)

Bis 2,4,6-trichlorophenyl malonate[71] (**54**)

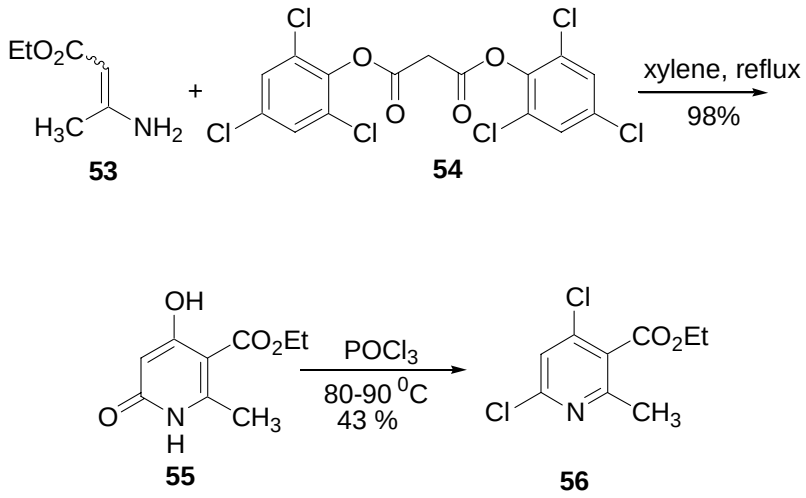
To a mixture of malonic acid (3 g. 28.84 mmol), 2,4,6-trichlorophenol (9.11 g, 46.14 mmol) was added $POCl_3$ (10 ml) at 0 °C dropwise. Then the reaction mixture was allowed to come to room temperature and heated at 120-130 °C over a period of 6-7 h. The resulting black solution was poured into ice-cold water slowly and stirred for 5 min. during which a brown precipitate was formed. The precipitate was filtered and repeatedly washed with water (5 times) and then dried in oven for 5 h (keeping oven temperature below 80 °C) to give 8.5 g (63.6 %) of the *title compound* **54**.

MP. 138-139 °C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (s, 4H), 4.05 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 140.3, 132.69, 129.4, 128.7, 39.6.

Ethyl 4,6-dichloro-2-methylnicotinate (56)



A stirred solution of 3-aminocrotonate (**53**) (1.29 g, 10 mmol) and bis-2,4,6-trichlorophenyl malonate[71] (**54**) (4.63 g, 10 mmol) in xylene (10 mL) was heated at reflux for 7-8 h. Then the reaction mixture was cooled to room temperature and kept for overnight during which a brown precipitate was formed. Filtration and washing with benzene 3-4 time to remove any 2,4,6-trichlorophenol gave 1.93 g of ethyl 4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (**55**), mp 225-228 ºC (lit.[72] 232 ºC) in 98% yield, which was used for the next step without further purification.

To the pyridone **55** (1.9 g, 9.6 mmol) was added $POCl_3$ (3.67 mL, 40 mmol) at 0 ºC and then heated on an oil bath keeping bath temperature fixed at 80-90 ºC. After 70 h at that temperature the resulting black solution was cooled to room temperature, poured into 50 mL of ice-cold water and extracted with CH_2Cl_2 (3-4 times). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over

anhydrous Na_2SO_4, concentrated and purified by column chromatography to give 980 mg (43%) of the title compound **56** as a yellow liquid.

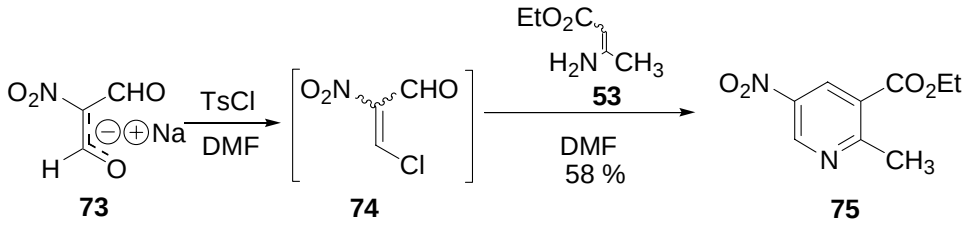
IR (CH_2Cl_2) 1730, 1552, 1275, 1224, 1147 cm.$^{-1}$

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (s, 1H), 4.42 (q, 2H, J = 7.2 Hz), 2.54 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 157.3, 151.0, 142.7, 128.0, 121.8, 62.2, 22.5, 13.9.

HRMS (ESI) calcd for $C_9H_{10}Cl_2NO_2$ $[M + H]^+$ *m/z* 234.0089 found 234.0081.

Ethyl 2-methyl-5-nitronicotinate (75)



73 **74** **75**

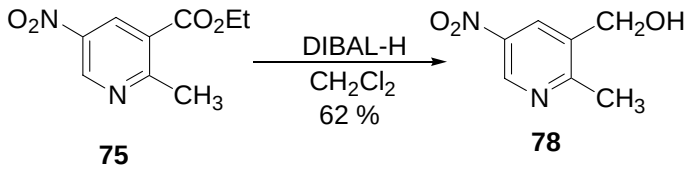
A solution of sodium nitromalonaldehyde monohydrate[78] (**73**) (1.5 g, 11.2 mmol) in dry DMF (4 mL) was dried over 4-Å molecular sieves (2 g) for 2 h, filtered, and the sieves were washed with DMF (2 mL) under argon. Pyridine (5 mL) was added to the filtrate and the red solution was cooled to –5 ˚C. A solution of *p*-toluenesulfonyl chloride (2.2 g, 11.2 mmol) in DMF (2 mL) was added dropwise, while the temperature was maintained below 0 ˚C. The solution became very viscous and was warmed to room temperature slowly. A solution of 3-aminocrotonate (**53**) (1.44 g, 11.2 mmol) in DMF (4

mL) was added dropwise and the resultant blood red solution was stirred for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and washed with 5% aqueous Na_2CO_3 solution, dried over anhydrous Na_2SO_4 and concentrated. The crude product on purification by column chromatography followed by crystallization gave 1.2 g (58%) of **75** as white crystalline needles: mp 62˚C (lit.[77] 63- 64 ˚C).

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.37 (d, 1H, *J* = 2.4 Hz), 8.91 (d, 1H, *J* = 2.4 Hz), 4.42 (q, 2H, *J* = 7.0 Hz), 2.93 (s, 3H), 1.42 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ 166.2, 164.2, 146.2, 142.1, 133.0, 125.8, 62.1, 25.0, 14.0.

(2-Methyl-5-nitropyridin-3-yl)methanol (78)



75 **78**

To a stirred solution of **75** (400 mg, 1.90 mmol) in dry CH_2Cl_2 (40 mL) was added 6.12 mL of diisobutylaluminum hydride (1 M solution in toluene) dropwise keeping the bath temperature fixed at -10 → -5 ˚C over a period of 10 min. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and stirred for 30 min at 0 ˚C. Then it was acidified with 10% HCl and the two layers so formed were separated. The aqueous layer was extracted with CH_2Cl_2 (twice), the combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and

purified by column chromatography (EtOAc:petroleum ether 30:70) to give 200 mg (62%) of *the title compound* **78** as a yellow crystalline solid: mp 165-167 ˚C.

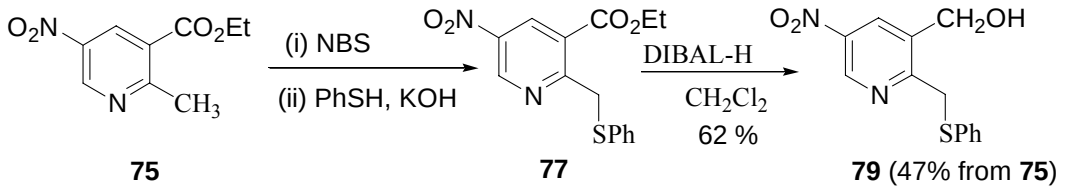
IR (KBr) 3197, 1595, 1519, 1354, 1052 cm.$^{-1}$

^{1}H NMR (300MHz, $CDCl_3$) δ 9.23 (d, 1H, *J* = 2.3 Hz), 8.58 (d, 1H, *J* = 2.3 Hz), 4.83 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (50MHz, $CDCl_3$:DMSO-d_6 10:1) δ 161.2, 142.2, 141.0, 136.2, 127.5, 59.0, 21.1.

MS (ESI) *m/z* (relative intensity) 210 ([M+CH_3CN]H $^{+}$, 47), 169 ([M+H]$^{+}$, 100).

{5-Nitro-2-[(phenylthio)methyl]pyridin-3-yl}methanol (79)



75 **77** **79** (47% from **75**)

(a) *Ethyl 5-nitro-2-[(phenylthio)methyl]nicotinate* (**77**)

Step 1 : A stirred mixture of compound **75** (420 mg, 2 mmol), N-bromosuccinimide (450 mg, 2.50 mmol), glacial acetic acid (0.12 mL), AIBN (2 mg) and carbon tetrachloride was illuminated with a 200 W lamp. After 6 h the reaction mixture was cooled to 0 ˚C and neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure quickly. The ethyl 2-(bromomethyl)-5-nitronicotinate (**76**) so formed was found to undergo rapid

polymerization; so, the crude compound was subjected to next the step without any further purification.

^{1}H NMR (200MHz, $CDCl_3$) δ 9.47 (d, 1H, *J* = 2.53 Hz), 9.02 (d, 1H, *J* = 2.48 Hz), 5.09 (s, 2H), 4.50 (q, 2H, *J* = 7.1 Hz), 1.47 (t, 3H, *J* = 7.0 Hz); the ^{1}H-NMR shows that **76** is contaminated somewhat with the starting material **75**.

Step 2 : To a solution of KOH (120 mg, 2.14 mmol) in ethanol (4 ml) was added thiophenol (0.2 mL, 2 mmol) and stirred for 15 min. This solution was added to a solution of bromo compound **76** in ethanol (8 mL) at 0 °C dropwise over a period of 15 min., during which the colour of the solution changes to deep red. After 1h, the red solution changes to orange and was allowed to attain room temperature and stirred overnight. Solvent was removed under reduced pressure, diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to give 600 mg of a mixture of **77** and **75** (80:20) (from ^{1}H NMR).

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.32 (d, 1H, *J* = 2.7 Hz), 8.92 (d, 1H, *J* = 2.6 Hz), 7.36-7.21 (m, 5H), 4.74 (s, 2H), 4.43 (q, 2H, *J* = 6.9 Hz), 1.44 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6, 164.0, 146.0, 142.5, 134.5, 133.7, 130.9, 128.8, 127.1, 125.9, 62.5, 39.8, 14.0.

(b) The above mixture underwent reduction by diisobutylaluminum hydride (6 mL, 6 mmol) (1 M solution in toluene) under the same condition as described for **78** to give 260 mg of the *title compound* **79** in 47% yield (from **75**) as a white crystalline solid: mp 94-96 °C.

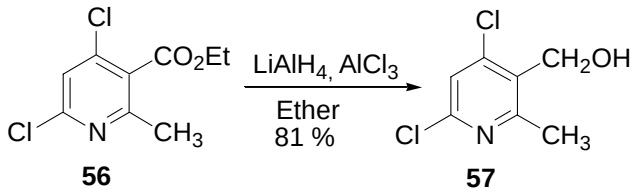
IR (KBr) 3443, 2316, 1583, 1516, 1354, 1042 $cm.^{-1}$

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.16 (d, 1H, *J* = 2.1 Hz), 8.64 (d, 1H, *J* = 2.1 Hz), 7.40-7.22 (m, 5H), 4.86 (s, 2H), 4.36 (s, 2H), 2.06 (bs, 1H, -O*H*).

^{13}C NMR (50 MHz, $CDCl_3$) 160.8, 143.4, 142.7, 136.0, 133.6, 131.4, 130.4, 129.1, 127.6, 60.5, 38.6.

MS (ESI) *m/z* (relative intensity) 277 ($[M+H]^+$, 100), 259 ($[M-H_2O]H^+$, 62).

(4, 6-Dichloro-2-methylpyridin-3-yl)methanol (57)



56 **57**

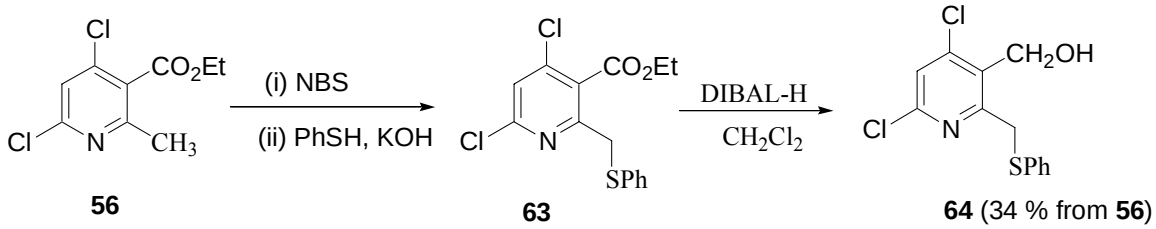
To a suspension of $LiAlH_4$ (50 mg, 1.42 mmol) in dry ether (10 mL) was added anhydrous $AlCl_3$ (190 mg, 1.42 mmol) at once at 0 °C under argon. The mixture was stirred for 5 min followed by the addition of ethyl 4,6-dichloro-2-methylnicotinate (**56**) (100 mg, 0.85 mmol) in ether (5 ml) at that temperature. The resulting mixture was

heated at reflux for 3-4 h, cooled to 0 °C and quenched carefully with saturated aqueous Na_2SO_4. Two layers were separated and the aqueous layer was extracted with ether 3-4 times. The combined ether layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to give 70 mg of the *title compound* **57** in 81% yield as yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (s,1H), 4.83 (s, 2H), 2.67 (s, 3H),1.97 (bs,1H, -O*H*).

^{13}C NMR (50 MHz, $CDCl_3$) δ 160.5, 149.5, 146.2, 130.4, 122.3, 58.0, 22.2.

{4,6-Dichloro-2-[(phenylthio)methyl]pyridin-3-yl}methanol (64)



56 **63** **64** (34 % from **56**)

(a) Ethyl 4,6-dichloro-2-[(phenylthio)methyl]nicotinate (**63**) was prepared from ethyl 4,6-dichloro-2-methylnicotinate (**56**) (240 mg, 1.02 mmol) as a mixture by the bromination followed by nucleophilic substitution of thiophenolate as described for **77**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51-7.15 (m, 6H), 4.54-4.35 (m, 2H), 4.29 (s, 2H), 1.49-1.32 (m, 3H).

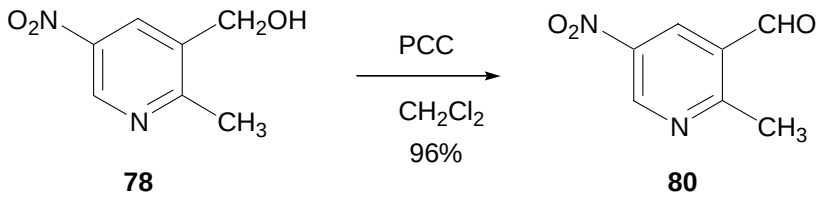
(b) **63** was reduced by $LiAlH_4$ in presence of $AlCl_3$ in ether to give the *title compound* **64** in 34% overall yield from **56** by following the same procedure as described for **79** as a yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55-7.20 (m, 6H), 4.80 (s, 2H), 4.35 (s, 2H), 2.20 (bs, 1H, -O*H*).

^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6, 149.8, 147.0, 133.6, 131.2, 129.9, 129.0, 127.5, 123.8, 57.9, 39.1.

HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NOS$ $[M + H]^+$ *m/z* 300.0017 found 300.0007.

2-Methyl-5-nitronicotinaldehyde (**80**)



78 **80**

To a stirred solution of **78** (200 mg, 1.19 mmol) in 20 ml of CH_2Cl_2 was added PCC (400 mg, 1.85 mmol) under argon and stirred for 1.5 h. The resulting black reaction mixture was filtered over a short pad of silica gel and Celite (1:1) using 30% (EtOAc : petroleum ether) as eluent to give 190 mg (96% yield) of the *title compound* **80** as a yellow crystalline solid: mp 64-65 ˚C.

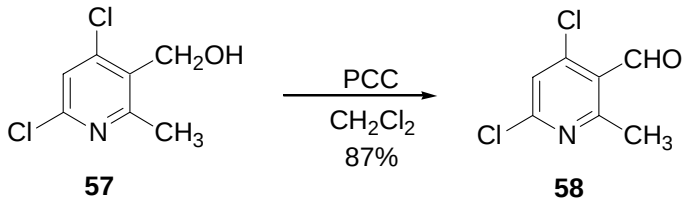
IR (KBr) 1702, 1575, 1354 cm.$^{-1}$

^{1}H NMR (200MHz, $CDCl_3$) δ 10.38 (s, 1H), 9.47 (d, 1H, *J* = 2.6 Hz), 8.86 (d, 1H, *J* = 2.5 Hz), 3.02 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 188.8, 165.9, 147.4, 142.8, 132.6, 128.9, 22.8.

MS (ESI) *m/z* (relative intensity) 185 ($[M+H_2O]H^+$, 100), 167 ($[M+H]^+$, 93).

4,6-Dichloro-2-methylnicotinaldehyde (58)



57 **58**

Following the similar procedure as described for **80**, 60 mg (87%) of the *title compound* was obtained by PCC oxidation starting from alcohol **57** (70 mg, 0.36 mmol) as a pale yellow solid: mp 42-44 °C.

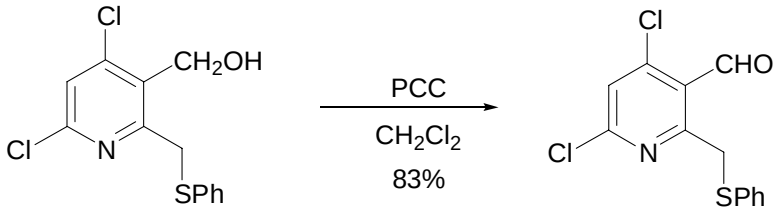
IR ($CHCl_3$) 1700, 1510, 1390, 1110 $cm.^{-1}$

^1H NMR (200 MHz, $CDCl_3$) δ10.56 (s, 1H), 7.33 (s, 1H), 2.75 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 189.4, 162.6, 153.8, 149.4, 125.0, 123.2, 24.1.

HRMS (ESI) calcd for $C_7H_6Cl_2NO$ $[M + H]^+$ *m/z* 189.9826 found 189.9834.

4,6-Dichloro-2-[(phenylthio)methyl]nicotinaldehyde (65)



64 **65**

Following the similar procedure as described for **80**, 25 mg (83%) of the *title compound* **65** was obtained by PCC oxidation of alcohol **64** (30 mg, 0.1 mmol) as a yellow oil.

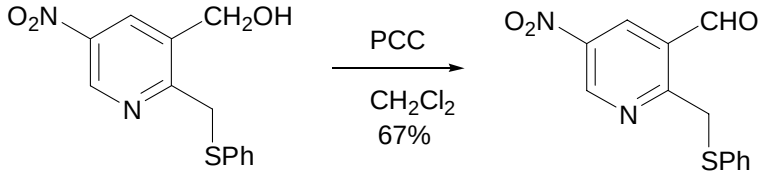
IR ($CHCl_3$) 1704, 1540, 1080 $cm.^{-1}$

^1H NMR (200 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.40-7.20 (m, 6H), 4.54 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 161.8, 153.8, 149.4, 134.5, 131.3, 128.8, 127.2, 124.8, 124.3, 38.7.

HRMS (ESI) calcd for $C_{13}H_{10}Cl_2NOS$ $[M + H]^+$ *m/z* 297.9860 found 297.9854.

5-Nitro-2-[(phenylthio)methyl]nicotinaldehyde (81)



79 **81**

was prepared by the PCC oxidation following the similar methodology as described for **80**, starting from **79** (150 mg, 0.54 mmol) in 67% yield as a bright yellow crystalline solid: mp 106-107 °C.

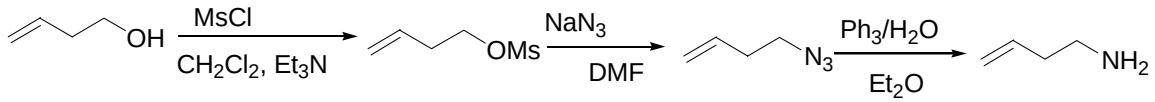
IR (KBr) 1704, 1576, 1353 $cm.^{-1}$

^{1}H NMR (200 MHz, $CDCl_3$) δ 10.16 (s, 1H), 9.41 (d, 1H, *J* = 2.4 Hz), 8.86 (d, 1H, *J* = 2.5 Hz), 7.50-7.14 (m, 5H), 4.66 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 187.4, 165.1, 147.3, 143.3, 133.0, 132.9, 132.0, 129.1, 128.0, 38.4.

MS (ESI) *m/z* (relative intensity) 316 ($[M+CH_3CN]H^+$, 10), 293 ($[M+H_2O]H^+$, 7), 275 ($[M+H]^+$, 100).

But-3-enenylamine



(a) To a stirred mixture of but-3-en-1-ol (6 g, 83.20 mmol), Et_3N (23.19 mL, 0.16 mol) and dry CH_2Cl_2 (85 mL) was added CH_3SO_2Cl (9.74 mL, 0.12 mol) dropwise at 0 °C. The mixture was then stirred for 1h at 0 °C and 2h at room temperature. Ice-cold water was then poured into it. Aqueous layer was separated and extracted with CH_2Cl_2 three times. The combined organic extracts were thoroughly washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was then purified by flash chromatography (silica gel, EtOAC-petroleum ether 50 : 50) to give corresponding mesylate as yellow liquid (12 g, 96 % yield).

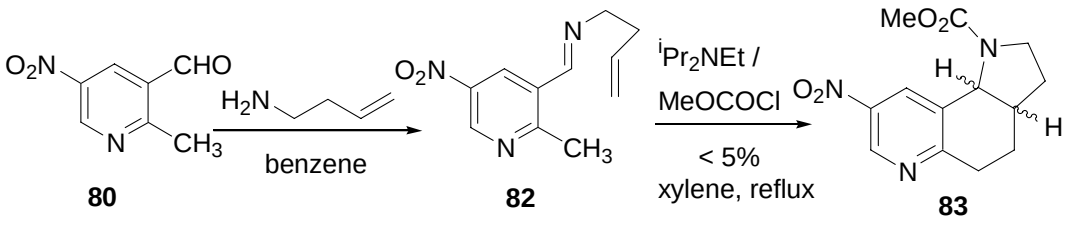
(b) NaN_3 (15.6 g, 0.24 mol) was added to a stirred solution of mesylate (12 g, 0.08 mol) in dry DMF (80 mL) at room temperature. The resulting mixture was stirred at same temparature for 1 day. It was then diluted with ether and water was added. The aqueous layer was separated and extracted with ether. The combined organic extracts were

thoroughly washed with water, brine and dried (Na_2SO_4). This ethereal solution of azide was used as it is for the next step.

(c) To the stirred ethereal solution of azide, Ph_3P (27.27 g, 0.10 mol) was added in one portion at 0 °C. After 1 h at 0 °C (gas evolution) and 1 h at room temperature, water (4 mL) was added. The resulting mixture was stirred at room temperature for 14 h. After that the reaction mixture was cooled to 0 °C. A solid mass separated out and 10% HCl was added dropwise to make the solution acidic. After that the resulting solution was filtered, washed with water and aqueous part was separated. Organic part was washed with water and the combined aqueous fractions were washed with small amount of ether and evaporated to dryness. The salt was suspended in ether, then cooled at 0 °C. The flask was equipped with a reflux condenser through which 40% aqueous KOH solution was added and the liberated amine was extracted with ether several times. Fresh beads of solid KOH were added to it and kept for 1 h. The aqueous layer was separated out, the upper amine layer was then separated and dried over a few beads of solid KOH until no further separation of aqueous layer occurred. The solution was decanted and distilled [long Vigreux column was used] to give but-4-enenylamine as a colourless liquid (3.2 g; 52 % overall yield).

^{1}H NMR (200 MHz, $CDCl_3$: CCl_4 7:3) δ 5.81-5.55 (m, 1H), 5.1-4.9 (m, 2H), 2.70 (t, J = 6.6 Hz, 2H), 2.2-2.05 (m, 2H).

Methyl 8-nitro-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*f*]quinoline-1-carboxyl-ate (83)



A stirred solution of aldehyde **80** (100 mg, 0.60 mmol) in benzene (5 mL) was treated with but-3-enylamine (90 mg, 1.25 mmol) at room temperature. After 1 h, to the reaction mixture was added anhydrous Na_2SO_4 (0.5 g) and stirred for another 2 h. The resulting mixture was filtered under argon, kept over molecular sieves (4-Å) for 12 h and then filtered. Benzene was removed under reduced pressure and the resulting imine **82** was characterized by ^{1}H NMR spectroscopy.

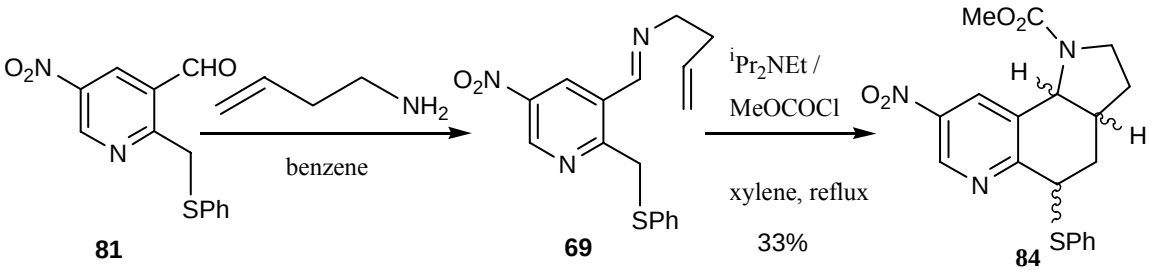
^{1}H NMR (200MHz, $CDCl_3$) δ 9.32 (bs, 1H), 8.91 (d, 1H, J = 2.3 Hz), 8.54 (bs, 1H), 5.90-5.73 (m, 1H), 5.14-5.05 (m, 2H), 3.92-3.61 (m, 2H), 2.82 (s, 3H), 2.50 (q, 2H).

The crude imine **82** was diluted with xylene (4 mL), cooled to 0 °C, and treated with diisopropylethylamine (0.21 mL, 1.2 mmol) followed by methyl chloroformate (0.09 mL, 1.2 mmol). After 40 min the reaction mixture was warmed to room temperature and heated to reflux for 4 h. The resulting black solution was cooled, solvent was removed under reduced pressure, diluted with CH_2Cl_2 and washed with 5% HCl (twice). The organic fragment was dried over anhydrous Na_2SO_4, concentrated and purified by preparative thin layer chromatography to give (5 mg, < 5%) of the title compound **83** as gummy liquid.

^{1}H NMR (300MHz, $CDCl_3$) δ 9.22 (d, 1H, *J* = 2.2 Hz), 8.85 (bs, 1H), 5.12 (bs, 1H), 3.82 (s, 3H), 3.64-3.36 (m, 2H), 3.08-2.98 (m, 1H), 2.78-2.69 (m, 1H), 2.22-1.97 (m, 4H).

LCMS *m/z* (relative intensity) 278 ($[M+H]^+$, 100).

Methyl 8-nitro-5-(phenylthio)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*f*]quinol-ine-1-carboxylate (**84**)



was prepared from aldehyde **81** (100 mg, 0.36 mmol) by following the same methodology as described for **83** in 34% yield as a gummy liquid.

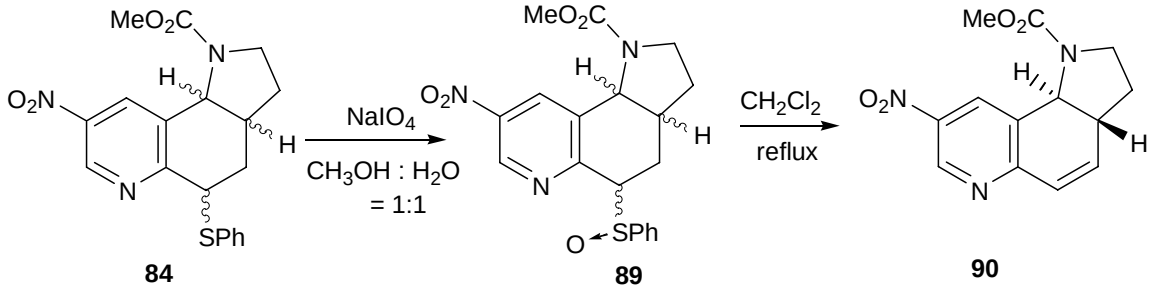
^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (d, 1H, *J* = 2.1 Hz), 8.56 (bs, 1H), 7.44-7.12 (m, 5H), 5.38 (d, 1H, *J* = 8.2 Hz), 4.72-4.65 (m, 1H), 3.83 (s, 3H), 3.49-3.39 (m, 2H), 3.05-2.85 (m, 2H), 2.58-2.41 (m, 1H), 2.30-2.10 (m, 2H), 1.95-1.75 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 162.0, 157.3, 143.8, 142.5, 133.6, 133.0, 132.8, 131.3, 129.0, 128.0, 56.8, 53.0, 48.6, 46.3, 31.8, 30.3, 29.6.

MS (ESI) *m/z* (relative intensity) 408 ($[M+Na]^+$, 100), 386 ($[M+H]^+$, 60), 339 ($[M-NO_2]^+$, 5), 314 (12), 301 (5), 276 ($[M-SPh]^+$, 22), 274 (15).

HRMS (ESI) calcd for $C_{19}H_{20}N_3O_4S$ $[M + H]^+$ *m/z* 386.1175 found 386.1161.

Methyl 8-nitro-2,3,3a,9b-tetrahydro-1*H*-pyrrolo[2,3-*f*]quinoline-1-carboxylate (90)



To a stirred solution of **84** (110 mg, 0.29 mmol) in 6 mL of methanol: water (1: 1) was added $NaIO_4$ (130 mg g, 0.60 mmol) portionwise. After the solution was stirred for 5-6 days at room temperature, water and CH_2Cl_2 were added and the aqueous layer was extracted with CH_2Cl_2. The combined organic fractions were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative thin layer chromatography (silica gel, ethyl acetate:petroleum ether 25 : 75) to give **55** as a yellow oil (20 mg) and sulfoxide **89** (70 mg). The sulfoxide **89** (70 mg) was then dissolved in CH_2Cl_2 (6 mL) and heated at reflux for 4 h. After concentration under reduced pressure, the crude product was purified by silica gel chromatography to give **90** (30 mg). The overall yield of **90** from **84** is 63%. Hydrochloride of **90** was made by passing dry HCl into the ethereal solution of **90** and was obtained as yellowish white solid. It may be mentioned that hydrochloride of **90** is highly hygroscopic: mp 159-160 ˚C.

IR (CH_2Cl_2) 1696, 1589, 1518, 1455, 1348 $cm.^{-1}$

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.21 (bs, 1H), 8.51 (bd, 1H), 6.73 (d, 1H, *J* = 10.0 Hz), 6.62-6.42 (m, 1H), 5.30 (d, 1H, *J* = 8.4 Hz), 3.78 (s, 3H), 3.72-3.45 (m, 1H), 3.43-3.20 (m, 1H), 3.19-2.90 (m, 1H), 2.37-2.17 (m, 1H), 1.95-1.65 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 156.5, 155.6, 144.0, 143.0, 137.8, 132.4, 130.0, 128.1, 57.4, 52.9, 45.4, 38.0, 31.0.

^{1}H NMR also run in C_6D_6; ^{1}H NMR (200 MHz, C_6D_6) δ 9.02 (d, 1H, *J* = 2.3 Hz), 8.70 (s, 1H), 6.51 (d, 1H, *J* = 9.6 Hz), 5.53-5.46 (m, 1H), 4.78 (d, 1H, *J* = 7.52 Hz), 3.36 (s, 3H), 3.12-2.75 (m, 2H), 2.12-1.85 (m, 1H), 3.19-2.90 (m, 1H), 1.37-1.02 (m, 2H).

MS (ESI) *m/z* (relative intensity) 317 ($[M+CH_3CN]H^+$, 8), 276 ($[M+H]^+$, 100), 214 (22), 199.0 ($[M-CO_2Me]^+$, 25), 158.0 (30).

HRMS (ESI) calcd for $C_{13}H_{14}N_3O_4$ $[M+H]^+$ *m/z* 276.0984; found 276.0989.

7. References

1. Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 1701.
2. For reviews, see: a) Martin, N.; Seoane, C; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237. (b) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199.
3. For reviews, see: (a) Chou, T.-S. *Rev. Heteroatom. Chem.* **1993**, *8*, 65. (b) Collier, S. J.; Storr, R. C. *In Progress in Heterocyclic Chemistry*: Gribble G. W.; Gilchrist, T. L. Eds. Pergamon: New York, 1988; Vol. 10, pp 25.
4. (a) Changeux, J.-P.; Bertrand, D.; Corringer, P. J.; Dehaene, S.; Edelstein, S.; Lena, C.; le Novère, N.; Marubio, L.; Picciotto, M.; Zoli, M. *Brain Res. Rev.* **1998**, *26*,198. (b) Karlin, A. *Nat. Res. Neurosci.* **2002**, *3*, 102.
5. (a) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4170. (b) Albuquerque, E. X.; Alkondon, M.; Pereira, E. F. R.; Castro, N. G.; Schrattenholz, A.; Barbosa, C. T. F.; Bonfante-Cabarcas, R.; Aracava, Y.; Eisenberg, H. M.; Maelicke, A. *J. Pharmacol. Exp. Ther.* **1997**, *280*, 1117. (c) Arias, H. R. *Biochim. Biophys. Act.* **1998***, 1376*, 173.
6. Cooper, E.; Couturier, S.; Ballivet, M. *Nature* **1990,** *350*, 235.
7. (a) Sharples, C. G. V.; Wonnacott, S. *Tocris Rev.* **2001**, No. 19, 1. (b) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, *6*, 465. (c) Lukas, R. J.; Changeux, J.-P.; le Novère, N. le, Albuquerque, E. X.; Balfour, D. J. K.; Berg, D. K.; Bertrand, D.; Chiappinelli, V. A.; Clarke, P. B. S.; Collins, A. C.; Dani, J. A.; Grady, S. R.; Kellar, K. J.; Lindstrom, J. M.; Marks, M. J.; Quik, M.; Taylor, P. W.; Wonnacott , S. *Pharmacol. Rev.* **1999**, *51*, 397. (d) Lloyd, K.G.; Williams, M.. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461. (e) Dani, J.A. *Biol. Psychiatry* **2001**, *49*, 166.

8. Matter, J. M.; Ballivet, M. *Neuronal Nicotinic Receptors. Experimental Pharmacology,* Clementi, F.; Fornasari, D.; Gotti, C. Eds. Vol 14. Springer, Berlin, 2000, 33–55.
9. Romanelli, M. N.; Fulvio, G. *Med. Res. Rev.* **2003**, *23*, 393.
10. Arneric, S. P., Brioni, J. D., Eds. Neuronal Nicotinic Receptors:Pharmacology and *Therapeutic Opportunities*; Wiley-Liss, Inc.:New York, 1999.
11. Paterson, D.; Nordberg, A. Neuronal nicotinic receptors in the human brain. *Prog. Neurobiol.* **2000**, 61, 75.
12. Levin, E. D., Ed. *Nicotinic Receptors in the Nervous System*; CRC Press: Boca Raton, FL, 2002.
13. Williams, M.; Arneric, S. P. *Exp. Opin. Invest. Drugs* **1996**, *5*, 1035.
14. Salín-Pascual, R. J.; Rosas, M.; Jimenez-Genchi, A.; Rivera-Meza, B. L.; Delgado-Parra, V. *J. Clin. Psychiatry* **1996**, *57*, 387.
15. Qian, C. G.; Li, T. C.; Shen, T. Y.; Libertine-Garahan, L.; Eckman, J.; Biftu, T.; Ip, S. *Eur. J. Pharmacol.* **1993**, *250*, R13.
16. Jensen, A. A.; Frølund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *45*, 4705.
17. Glennon, R. A.; Dukat, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1841.
18. Sharples, C. G.; Karig, G.; Simpson, G. L.; Spencer, G. A.; Wright, E; Millar, N. S.; Wannacott, S.; Gallagher, T. *J. Med. Chem*. **2002**, *46*, 3235.
19. McDonald, I. A.; Vernier, J. –M.; Cosford, N.; Corey-Naeve, J. *Curr. Pharm. Design* **1996**, *2*, 357.

20. Buccafusco, J. J.; Jackson, W. J.; Terry, A. V., Jr.; Marsh, K. C.; Decker, M. W.; Arneric, S. P. *Psychopharmacol.* **1995**, *120*, 256.

21. (a) Blanco, M. -J.; Paleo, M. R.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786. (b) Vale, C.; Vilaró, T.; Rodríguez-Farré, E.; Suñol, C. *J. Neurosci. Res.* **1999**, *57*, 95. (c) Conti, P.; De Amici, M.; De Micheli, C. *Farmaco* **2000**, *55*, 162.

22. (a) Virgilio, A. A.; Ellman, J. A. *Comb. Chem. Mol. Diversity Drug Discovery*; Gordon E. M. & Kerwin, J. F., Jr. Eds.; Wiley-Liss: New York, 1998, p 133-149. (b) Pohlmann, A. R.; Quirion, J. -C.; Guillaume, D.; Husson, H. P. *Quim. Nova* **1999**, *22*, 828. (c) Kim, H. –O.; Nakanishi, H.; Lee, M. S.; Kahn, M. *Org. Lett.* **2000**, *2*, 301. (d) Koch, K. N.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 1881.

23. (a) Lohof, E.; Burkhart, F.; Born, M. A.; Planker, E.; Kessler, H. *Adv. Amino Acid Mimetics Peptidomimetics* **1999**, *2*, 263. (b) Terada, Y.; Misoi, R.; Watanabe, N.; Hornberger, M.; Kreis, W. *Chem. Pharm. Bull.* **2000**, *48*, 349.

24. (a) Krayevsky, A. A.; Watanabe, K. A. *Nucleosides Nucleotides* **1993**, *12*, 649. (b) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Hernandez, S.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119. (c) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000,** *65*, 685.

25. Pressova, M.; Endova, M.; Tocik, Z.; Liboska, R.; Rosenberg, I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1225.

26. (a) Steffens, R.; Leumann, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 11548. (b) Singh, S. K.; Kumar, R.; Wengel, J. *J. Org. Chem.* **1998**, *63*, 10035. (c) Lescrinier, E.; Esnouf, R.; Schraml, J.; Busson, R.; Heus, H. A.; Hilbers, C. W.; Herdewijn, P. *Chem. Biol.* **2000**, *7*, 719.

27. Yamamoto, K.; Sun, W. Y.; Ohta, M.; Hamada, K.; DeLuca, H. F.; Yamada, S. *J. Med. Chem.* **1996**, *39*, 2727.

28. Grese, T.A.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shetler, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272

29. Kappe, C. O.; Peters, K.; Peters, E. –M. *J. Org. Chem.* **1997**, *62*, 3109.

30. Sarkar, T. K.; Basak, S.; Slanina, A.; Chow, T. J. *J. Org. Chem*. **2003**, *68*, 4206

31. Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125.

32. Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492.

33. (a) Kanne, D. B.; Ashworth, D. J.; T., C. M.; Mutter, L. C. *J. Am. Chem. Soc.* **1986**, *108*, 7864. (b) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506.

34. Glassco, W.; Suchocki, J.; George, C.; Martin, B. R.; May, E. L. *J. Med. Chem.* **1993**, *36*, 3381.

35. Vernier, J.-M.; Holsenback, H.; Cosford, N. D. P.; Whitten, J. P.; Menzaghi, F.; Reid, R.; Rao, T. S.; Scaan, A. I.; Lloyd, G. K.; Suto, C. M.; Chavez-Noriega, L. E.; Washburn, M. S.; Urrutia, A.; McDonald, I. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2173.

36. Meijler, M. M.; Matsushita, M.; Altobell, L. J., III; Wirsching, P.; Janda, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 7164.

37. (a) Xu, Y. -z.; Choi, J.; Calaza, M..; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (b) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861.

38. Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291.

39. Ullrich, T.; Krich, S.; Binder, S.; Mereiter, K.; Anderson, D. J.; Meyer, M. D.; Pyerin, M. *J. Med. Chem.* **2002**, *45*, 4047.

40. (a)Yang, X.; Luo, S.; Fang, F.; Liu, P.; Lu, Y.; He, M.; Zhai, H. *Tetrahedron* **2006**, *62*, 2240. (b) Zhai, H.; Liu, P.;Luo, S.; Fang, F.; Zhao, M. *Org*. *Lett*. **2002**, *4*, 4385.

41. Tønder, J. E.; Olesen, P. H. *Curr. Med. Chem*. **2001**, *8*, 651.

42. Beers, W. H.; Reich, E. *Nature* **1970**, *228*, 917.

43. Gund, R. M.; Spivak, C. E. *Methods Enzymol.* **1991**, *203*, 677.

44. Pullman,A.; Port, G. N. J. *Theor. Chim. Acta* **1973**, *32*, 77.

45. Barrett, A. N.; Roberts, G. C. K.; Burgen, A. S. V.; Clore, G. M. *Mol. Pharmacol*. **1983**, *24*, 443.

46. Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc*. **1984**, *106*, 1018.

47. Taylor, R.; Versichel, V. *J. Am. Chem. Soc*. **1983**, *105*, 5761.

48. Sheridan, R. P.; Nilakantan, R.; Dixon, J. S.; Venkataraghavan, R. *J. Med. Chem.* **1986**, *29*, 899.

49. Manallack, D. T.; Gallagher, T.; Livingstone, D. J. In *Neural Networks in QSAR and Drug Design*, Devillers, J., Eds.; Academic Press: London, **1996**; pp. 177-208.

50. Tønder, J. E.; Hansen, J. B.; Begtrup, M.; Pettersson, I.; Rimvall, K.; Christensen, B.; Ehrbar, U.; Olesen, P. H. *J. Med. Chem.* **1999**, *42*, 4970.

51. Olesen, P. H.; Tønder, J. E.; Hansen, J. B.; Hansen, H. C.; Rimvall, K. *Bioorg. Med. Chem.* **2000**, *8*, 1443.

52. Tønder, J. E.; Olesen, P. H.; Hansen, J. B.; Begtrup, M.; Pettersson, I. *J. Compu. - Aided Mol. Des.* **2001**, *15*, 247.

53. Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217.

54. Glennon, R. A.; Herndon, J. L.; Dukat, M. *Med. Chem. Res.* **1994**, *4*, 461.

55. Kim, K. H.; Lin, N.-H.; Anderson, D. J. *Bioorg. Med. Chem.* **1996,** *12,* 2211.

56. Dukat, M.; Dowd, M.; Damaj, M. I.; Martin, B.; El-Zahabi, M. A.; Glennon, R. A. *Eur. J. Med. Chem.* **1999**, *34*, 31.

57. Nicolotti, O.; Canu Boido, C.; Sparatore, F.; Carotti, A. *Farmaco* **2002**, *57*, 469.

58. (a) Nicolotti, O.; Pellegrini-Calace, M.; Carrieri, A.; Altomare, C.; Centeno, N. B.; Sanz, F.; Carotti, A. *J. Comput-Aid. Mol. Des.* **2001**, *15*, 859. (b) Nicolotti, O.; Pellegrini-Calace, M.; Altomare, C.; Carotti, A.; Carrieri, A.; Sanz, F. *Curr. Med. Chem*. **2002,** *9*, 1.

59. Jozwiak, K.; Ravichandran, S.; Collins, J. R.; Wainer, I. W. *J. Med. Chem.* **2004,** *47,* 4008.

60. Lin, N.-H.; Gunn, D. E.; Li, Y.; He, Y.; Bai, H.; Ryther, K. B.; Kuntzweiler, T.; Donnelly-Roberts, D. L.; Anderson, D. J.; Campbell, J. E.; Sullivan, J. P.; Arneric, S. P.; Holladay, M.W. *Bioorg. Med. Chem. Lett*. **1998,** *8*, 249.

61. Lin, N.-H.; Li, Y.; He, Y.; Holladay, M. W.; Kuntzweiler, T.; Anderson, D. J., Campbell, J. E.; Arneric, S. P. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 631.

62. Holladay, M. W.; Lebold S.A.; Lin, N.-H. *Drug Dev. Res.* **1995**, *35*, 191.

63. Parker M. J.; Beck, A.; Luetje, C. W. *Mol. Pharmacol.* **1998**, *54*, 1132.

64. Elmore, D. E.; Dougherty, D. A. *J. Org. Chem.* **1997**, *62*, 3109.

65. Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *37*, 3889.

66. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

67. Leusink, F. R.; ten Have, R.; van den Berg, K. J.; van Leusen, A. M.. *J. Chem. Soc. Chem. Commun.* **1992**, 1401.

68. Sarkar, T. K; Basak, S.; Wainer, I.; Moaddel, R.; Yamaguchi, K.; Chen, H-T.; Lin, C.-C. *J. Med. Chem*. **2004**, *47*, 6691.

69. Moaddel, R.; Jozwiak, K.; Yamaguchi, R.; Cobello, C.; Whittington, K.; Sarkar, T. K.; Basak, S.; Wainer, I. W. *J. Chromatogr. B* **2004**, *813*, 235.

70. Soliman. F. S. G.; Kappe, T. *Pharmazie* **1977**, *32*, 278

71. Kappe, T. *Monatsh. Chem*. **1967**, *98*, 674.

72. (a) Kappe, T.; Stelzel, H. P.; Ziegler, E. *Monatsh. Chem*. **1983**, *114*, 953. (b) Ziegler, E.; Hradetzky, F. *Monatsh. Chem*. **1964**, *95*, 1247.

73. Stadlbauer, W.; Fiala, W.; Fischer, M.; Hojas, G. *J. Prakt. Chem*. **2000**, *342*, 33.

74. Newkome, G. R.; Lee, H.-W. *J. Org. Chem*. **1982**, *47*, 2801.

75. Clarke, K.; Goulding, J.; Scrowston R. M. *J. Chem. Soc. Perkin Trans. I* **1984**, 1501.

76. Denzel, T., Höhn H. *J. Heterocyclic Chem*. **1977**, *14*, 813.

77. Hoffman, J. M.; Phillips, B.T.; Cochran, D. W. *J. Org. Chem*. **1984**, *49*, 193.

78. Fanta, P. E. "*Organic Synthesis*"; Wiley: New York, 1963; Collect. Vol. IV, pp 844.

79. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc*. **1982**, *104*, 7609.

80. Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc*. **1984**, *106*, 7175.

81. Lübbecke, H.; Boldt, P. *Tetrahedron* **1978**, *34*, 1577.